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Cerebral Hemoglobin Oxygen Saturation in Patients With Restless Legs Syndrome and Periodic Limb Movements in Sleep.

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CEREBRAL HEMOGLOBIN OXYGEN SATURATION IN PATIENTS WITH RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENTS IN SLEEP

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Abstract

Pathogenic theories of Restless Legs Syndrome (RLS) and Periodic Limb Movements in Sleep (PLMS) were reviewed and critiqued, and a new theory for the pathogenesis of RLS and PLMS was presented. It was proposed that both disorders are caused by sleep-related hypoperfusion in the area of the cerebral cortex that mediates sensation and movement in the legs. The hypoperfusion was proposed to be caused by high amplitude oscillations in total cerebral blood flow known as B-waves and by flow-reducing turbulence at several of the bifurcations in the anterior cerebral artery. This theory was tested by using near infra-red spectroscopy (NIRS) to measure cerebral hemoglobin oxygen saturation and total blood flow in three groups of subjects: nine patients with RLS, six patients with PLMS, and eleven age-matched control subjects. Cerebral oximetry was performed during both wakefulness and sleep. Polysomnography was used to assess sleep. It was predicted that high amplitude B-waves would occur in the RLS subjects during wakefulness, and in both RLS and PLMS subjects during sleep. In addition, it was predicted that the abnormal sensations and movement in RLS patients and the PLMS in both RLS and PLMS patients would occur during the B-wave troughs in cerebral hemoglobin

oxygen saturation. As expected, significant differences among the groups in abnormal leg sensations and leg movements while awake, and periodic leg movements while asleep were found. However, the results did not support the proposed theory. Although there was a statistically significant non-random occurrence of abnormal sensations and movements (both waking RLS movements and PLMS) in the B-wave cycle, the tendency was for these events to occur at both B-wave peaks and troughs. B-wave amplitudes and cerebral hemoglobin oxygen saturation levels were not significantly different among the three groups. There were also no significant differences within the RLS and PLMS groups in hemoglobin oxygen saturation levels at event onset as compared to periods when no events were present. Future studies should attempt to replicate the previous research that has implicated circulatory insufficiency in the pathogenesis of both disorders.

Introduction

Restless legs syndrome (RLS) is a neurological disorder characterized by the appearance of lower leg paresthesias during periods of prolonged motor inactivity. The symptoms appear most commonly in the evening, and are relieved by movement of the legs. Because the paresthesias (and subsequent motor hyperactivity) are most prominent as the patient attempts to fall asleep, chronic insomnia and sleep deprivation often occur in more severely affected patients.

Almost all patients who have RLS also have periodic limb movements in sleep (PLMS), which are stereotypic movements of the feet and lower legs that occur at semi-periodic intervals of between 20 and 40 seconds. The movements are generally restricted to non-rapid eye movement (NREM) sleep. Videotaped analyses of these movements have shown that they appear similar to the abnormal plantar reflex or Babinski response (Smith, 1985). The movements may cause brief arousals from sleep, and thus impair sleep quality, although it is also common for affected patients to have no sleep complaints. For example, Kales et al. (1982) studied 200 patients with complaints of insomnia and 100 control subjects without any sleep complaints. The prevalence of PLMS was exactly

the same (11%) in both groups, suggesting that approximately half of all subjects who have PLMS do not have a sleep complaint. Although about 90% of RLS patients have PLMS (Montplaisir, Godbout, Pelletier, and Warnes, 1994), many persons who have PLMS do not have RLS. For example, Guilleminault, Raynal, Weitzman, and Dement (1975) found that only two of sixteen insomniacs (12.5%) who had PLMS also had RLS. Despite this, because most RLS patients also have PLMS, and because many treatments which are effective for RLS are also effective for PLMS (e.g. dopamine and opioid agonists), it is generally accepted that the pathogenic mechanisms of the two disorders are closely related.

The pathogenesis of these two disorders remains unknown (Montplaisir, Godbout, Pelletier, and Warnes 1994; O'Keeffe, 1996), although four pathogenic theories of RLS, and two pathogenic theories of PLMS have been discussed with somewhat greater frequency. The pathogenic theories of RLS include reduced peripheral blood flow, peripheral neuropathy, central dopaminergic dysfunction, and central opioid neurotransmitter dysfunction. Reduced peripheral blood flow has also been proposed as a pathogenic mechanism for PLMS. Other pathogenic theories of PLMS include oscillations of reticular system excitability and

spontaneously occurring Babinski responses. In general, these theories are vague and poorly developed. A critical review shows that there is very little direct evidence to support any of them. Furthermore, none of these theories seem to be able to account for all of the well-established features of either disorder.

Even though the pathogenic mechanisms of RLS and PLMS remain unknown, effective treatments for both disorders are available. These include correction of anemia, opioid agonists, dopamine agonists, benzodiazepines (especially clonazepam), clonidine, and the anti-convulsants carbamezapine and gabapentin. The discovery of the effectiveness of these drugs has often come about through chance observation or through empirical trial and error investigation in single patients. Because the pathogenesis of RLS and PLMS remains unknown, the mechanisms by which these drugs exert their therapeutic effect is also unknown (correction of anemia being the apparent exception to this). This is problematical because many of these drugs can have serious side effects, and because it is possible that the therapeutic effect of these drugs arises from a secondary or non-specific effect, such as their sedative effects or their effects on cerebral blood flow, rather than their primary effect

(e.g. increasing dopamine levels in the case of dopamine agonists).

In this paper a new theory for the pathogenesis of RLS and PLMS will be presented. Briefly, it is proposed that both disorders are caused by sleep-related changes in cerebral blood flow which lead to periodic cerebral ischemia and hypercapnia that are most prominent in the distal territory perfused by the callosomarginal branches of the anterior cerebral arteries. This territory includes the somatosensory cortex for the feet and lower legs. It is further suggested (in agreement with Smith's spontaneous Babinski response theory of PLMS) that this cortical ischemia causes the normal descending pyramidal tract inhibition of the Babinski response to be periodically released, resulting in the spontaneous and periodic occurrence of the reflex. The ability of this periodic cerebral ischemia theory (the PCI theory) to account for all of the well-established features of both RLS and PLMS will be briefly discussed.

One important implication of the PCI theory that will also be discussed concerns the treatment of RLS and PLMS. The proposed PCI theory suggests that cerebral vasodilators should be the most effective means of treatment for both disorders, and further that the drugs

which have been found to be beneficial (e.g. L-dopa, clonazepam) exert their therapeutic effect by either increasing cerebral blood flow or by reducing the amplitude of the oscillations in cerebral blood flow (B-waves) that are proposed to be one of the physiological bases of both disorders. Thus, vasodilators have the potential for offering a more effective means of treating RLS and PLMS.

The present study was an attempt to test this new theory of RLS and PLMS by recording cerebral hemoglobin oxygen saturation levels during wakefulness and sleep in three groups of subjects: RLS patients, PLMS patients, and control subjects without any sleep complaints. It was predicted that both RLS and PLMS patients would have oscillations of total cerebral blood flow and cerebral oxyhemoglobin levels (i.e. B-waves) when symptoms were present. It was further predicted that the waking sensory and motor symptoms in RLS patients, and the PLMs during sleep in RLS and PLMS patients, would occur at the troughs of the cyclic oscillations of cerebral oxyhemoglobin levels (i.e. when cerebral oxyhemoglobin levels were at their lowest).

Restless Legs Syndrome (RLS) and Periodic Limb Movements in Sleep (PLMS): A Brief Review

Clinical Features

Restless legs syndrome was first described by Willis (1685), but was almost unknown to the modern medical community until 1944 when Karl Ekbom described a series of eight cases (K. A. Ekbom, 1944). Ekbom later described several larger case study series in extensive detail (K. A. Ekbom, 1945, 1960, 1970). Other excellent reviews of the clinical features of RLS have been presented by several authors (Gorman, Dyck, and Pearson, 1965; Morgan, 1967; Walters, 1995; Young, Humphries, and DeWolfe, 1969), and the following description of the clinical features of RLS is based on these reviews.

Although the name "Restless Legs Syndrome" is suggestive of a motor disorder, RLS is characterized by both sensory and motor symptoms. The sensory symptoms consist primarily of a difficult-to-describe lower leg paresthesia. Terms used most often to describe the sensations include "creeping," "crawling," "pulling," "prickling," etc.. These sensations are usually reported to occur deep within the leg muscles rather than on the surface of the skin. A review of the symptomatology of 112 RLS patients by K. A. Ekbom (1945) found that 98% of

patients had paresthesias in the lower legs (between the ankle and knees), 27% had paresthesias in the thighs, 15% had paresthesias in the feet, and 6% had paresthesias in the arms. Patients who had paresthesias in the arms often did not have them in the hands. The paresthesias are usually bilateral, but may be worse or appear exclusively on one side. Some patients do report having pain in addition to the paresthesias, usually of a dull aching quality (K. A. Ekbom, 1944, 1945; Young et al., 1969). In fact, in his 1945 monograph, K. A. Ekbom initially divided RLS into separate painful and paresthetic forms. However, he did not maintain this distinction in his later reviews (K. A. Ekbom, 1960, 1970). Finally, some RLS patients also complain of cold legs and feet (Ancoli-Israel, Seifert, and Lemon, 1986; K. A. Ekbom, 1945; Ware, Blumoff, and Pittard, 1988).

One of the most characteristic features of RLS is that the sensory symptoms appear almost exclusively during periods of prolonged motor inactivity. Another characteristic feature is that movement of the legs provides temporary relief from the paresthesias. This relief may be partial or complete, and is usually effective only when the patient is actually engaging in movement and for a relatively short time after the

movement has been stopped. Although it is generally accepted that RLS patients move their legs to gain relief from their paresthesias, a study by Pelletier, Lorrain, and Montplaisir (1992) found that only about half of the recorded waking leg movements in RLS patients were associated with sensory events, while almost all sensory events were associated with leg movements. Thus, waking movements in RLS patients may occur in the absence of any sensory event. Pelletier et al. concluded that the sensory and motor events in RLS were independent manifestations of a common underlying pathogenic mechanism. Finally, there is a definite circadian periodicity to the appearance of RLS symptoms; regardless of whether they occur in the waking or sleep state, they are most common in the late evening and during the night (Becker, Jamieson, and DeLaCueva, 1993; Walters, Trenkwalder, Hening, Chokroverty, and Rahman, 1995).

The motor symptoms in RLS consist primarily of excessive voluntary motor activity such as rubbing or massaging the legs, rubbing the legs together while in bed, and (eventually) getting out of bed and walking around. The motor activity usually has an agitated or restless quality. In older and more severely affected patients, waking myoclonic twitches of both upper and

lower extremities may be present (Walters, Hening, and Chokroverty, 1988). Some studies have also found that RLS patients may have periodic movements of the feet and lower legs while awake (Pollmacher and Schulz, 1993; Walters et al, 1988), although it is unclear from these reports if these movements are similar to the PLMs that occur during sleep. Finally, about 80 to 90 percent of RLS patients have PLMS during sleep (Coccagna and Lugaresi, 1981; Montplaisir, Lapierre, Warnes, and Pelletier, 1992).

Although many authors have emphasized that RLS can produce severe and chronic insomnia (e.g. K. A. Ekbom, 1945; 1960; Gorman et al., 1965; Morgan, 1967; Walters, 1995), there is surprisingly little quantitative data available on this subject. For example, no studies have been published in which the nocturnal sleep parameters of RLS patients have been compared to those of normal subjects. In an attempt to address this issue, one must turn to the RLS treatment studies in which polysomnography was performed under either baseline or placebo conditions. Three such studies (Trenkwalder et al., 1995; Wagner et al., 1996; and Zucconi et al., 1989) will be briefly mentioned here. Trenkwalder et al. studied 28 RLS subjects under placebo and treatment conditions, and reported a mean sleep latency of 70 minutes for the

placebo condition. Wagner et al. studied ten RLS patients under baseline, placebo, and treatment conditions, and reported a mean sleep latency of 47.4 minutes and a mean sleep efficiency (defined as the percentage of time in bed spent in sleep) of 72.0% for the baseline condition. Zucconi et al. studied nine RLS patients and reported a mean sleep latency of 37.5 minutes and a mean sleep efficiency of 57.0% under baseline conditions. When compared to normative values published by Bixler, Kales, Jacoby, Soldatos, and Vela-Bueno (1984) (sleep latency - 22.1 minutes, sleep efficiency - 88.1%), the values in the three studies above are clearly indicative of insomnia.

The first description of periodic limb movements in sleep (PLMS) is generally attributed to Symonds (1953) who described five patients with a variety of motor abnormalities in sleep. Although Symonds noted that his patients had nocturnal leg movements, he did not record these movements polygraphically or observe them visually, and he was apparently unaware of their periodic nature. At least two of his patients also apparently had either waking or nocturnal epileptic seizures, a finding which led Symonds to conclude that PLMS was caused by epileptic activity. Symonds used the term "nocturnal myoclonus" to describe his patients' abnormal motor activity. This term

persisted until the early 1980s, and was replaced with the term "periodic limb movements in sleep" after the periodic nature of the movements had become well established, and after it had been shown that the movements were neither myoclonic seizure activity nor exclusively nocturnal in occurrence (Coleman et al., 1980; Guilleminault, Raynal, Weitzman, and Dement, 1975; Lugaresi, Coccagna, Ceroni, and Ambrosetto, 1968). The studies by Guilleminault et al. and Lugaresi et al. failed to support Symonds' hypothesis that the movements were associated with epileptic activity.

Lugaresi et al. (1968) were the first to record PLMs polygraphically, and to emphasize their periodic nature. Their initial recordings of PLMS were in patients with RLS, but they soon found that PLMS could occur in patients without RLS or sleep complaints. Their recordings showed that the movements occurred at semi-periodic intervals of between 20 and 40 seconds, and that they were generally bilateral, simultaneous, and occurred primarily in the legs. They also noted that the movements were most common in light NREM sleep (Stages 1 and 2), and were often accompanied by brief electroencephalographic (EEG) arousals from sleep. A recent study by Pollmacher and Schulz (1993) found that PLMs were most frequent during

wakefulness and sleep Stages 1 and 2, less frequent in Stages 3 and 4 (slow wave sleep), and relatively uncommon in rapid eye movement (REM) sleep. They also found that the inter-movement-interval (IMI) was shortest during wakefulness and Stage 1 (mean IMIs of 33.3 and 34.4 seconds respectively), got longer during NREM stages 2, 3, and 4 (combined IMI of 41.0 seconds), and was longest during REM sleep (mean IMI 53.2 seconds). The movement duration was longest during wakefulness (2.9 seconds) and Stage 1 (2.6 seconds), got progressively shorter during NREM stages 2, 3, and 4 (2.3 seconds), and was shortest in REM sleep (1.8 seconds). Thus, the movements were clearly too long to be considered myoclonic. An examination of IMI distributions for both groups of PLMS patients (Kayed, Roberts, and Davies, 1990) and individual patients (Montplaisir et al., 1985) shows that the modal IMI is often in the 20 to 30 second range, and that the mean IMI is usually higher than this because of outliers at the upper end of the distribution.

Two studies have provided detailed descriptions of PLMs based on videotaped analyses of the movements (Guilleminault et al., 1975; Smith, 1985). Guilleminault et al. reported that the movements consisted of "a rapid partial flexion of the foot at the ankle, extension of the

big toe, and partial flexion at the knee and hip..." (Guilleminault et al., 1975, p. 19). Smith (1985) found results that were very similar to those obtained by Guilleminault et al.. Smith reported that 91% of the PLMs he recorded were characterized by dorsiflexion of the foot at the ankle, 82% showed dorsiflexion and fanning of the small toes, 72% showed dorsiflexion of the big toe, and 28% showed partial flexion of the leg at the knee and hip. Smith pointed out that this pattern of movements was similar in appearance to the abnormal plantar reflex (Babinski's response), and he proposed that PLMs were in fact spontaneously occurring Babinski responses which occurred because of a reduction in supraspinal inhibition of lower motor neurons during NREM sleep.

Several different sets of scoring criteria have been used to score PLMs over the years, and unfortunately, none of them have been empirically derived. Guilleminault et al. (1975) scored any movement as a PLM if it had a duration of between 0.5 and 15 seconds and an IMI of less than 120 seconds. In addition, each movement had to part of a series of at least three such movements. Coleman, Pollak, and Weitzman (1980) scored movements as PLMs if they were between 0.5 and 4.5 seconds in duration, had an IMI of between 20 and 40 seconds, and were part of series

of at least five such movements. Coleman (1982) later modified his criteria such that any movement which was 0.5 to 5.0 seconds in duration with an IMI of between 5 and 90 seconds, and part of a series of four such movements was scored as a PLM. Several years earlier, the Association of Sleep Disorders Centers (ASDC, 1979) used movement duration criteria of 0.5 to 10 seconds, and IMI criteria of 5 to 120 seconds in its diagnostic criteria for nocturnal myoclonus. In addition, three separate series of at least 30 PLMs each had to be present for a diagnosis of nocturnal myoclonus to be given. Finally, the American Sleep Disorders Association (ASDA, 1993) has recently published a set of guidelines and scoring criteria for recording and scoring PLMs. These criteria are recognized as the current standard, and are a revision of those presented earlier by Coleman (1982). Briefly, PLMs are recorded polygraphically by placing two small surface electrodes over the anterior tibialis muscle (the primary muscle involved in flexion of foot). The scoring criteria can be summarized as follows: 1) each movement must be part of a series of at least four PLMs, 2) the movement duration must be between 0.5 and 5.0 seconds, and 3) the IMI must be between 5 and 90 seconds. Movements which occur at the end of respiratory events (i.e. apneas and

hypopneas) are not counted as PLMs. The number of PLMs per hour of sleep (the PLM index or PLMi) is tabulated, and five or more movements per hour of sleep is considered abnormal.

As noted above, these criteria have not been derived from an empirical analysis of the temporal characteristics of PLMs, but instead reflect the consensus of various researchers familiar with this disorder. The current ASDA criteria can be criticized for being somewhat liberal in both the IMI and number of movements in a series criteria. For example, according to these criteria, four movements with IMIs of 7, 90, and 30 seconds would be scored as PLMs, despite the obvious lack of any consistent periodicity in their IMIs. Given this somewhat liberal definition of PLMs, the diagnostic criterion for the PLMi of five or more events per hour of sleep also seems liberal, and it is possible that it may be resulting in a significant number of false positive PLMS diagnoses.

The issue of whether or not PLMS leads to daytime sleepiness or to nocturnal sleep disruption has received much attention over the years. The early descriptive study by Guilleminault et al. (1975) was based on PLM data from 16 patients who were part of a total sample of 140 patients who were referred for evaluation of insomnia.

These 16 patients thus represented 11.4% of the total sample, a finding which led Guilleminault to conclude that PLMS could be an important cause of insomnia [122]. The association of PLMS with insomnia in some patients, and its well known association with RLS seemed to indicate that it might always represent a pathological (or sleep disrupting) finding. However, it was soon shown that PLMS could occur in a variety of sleep disorders (such as narcolepsy and sleep apnea), and that its prevalence in these disorders was not significantly different from its prevalence in insomnia (Coleman et al., 1980). Moreover, a study by Kales et al. (1982) also showed that the prevalence of PLMS in insomnia was not significantly different from its prevalence in normal subjects. Other work has shown that the PLM arousal index (PLMAi) is poorly correlated with subjective sleep complaints (Ancoli-Israel et al., 1991; Dickel and Mosko, 1990), and has either low correlations (Coleman, Bliwise, et al., 1982) or is not correlated (Mendelson, 1996) with the average sleep latency on the Multiple Sleep Latency Test (MSLT), an objective test of sleepiness.

It is clear from these studies that PLMS is often not associated with subjective sleep complaints or with objective evidence of abnormal sleep or excessive daytime

sleepiness. Because of this, a distinction is usually made between periodic limb movements in sleep (PLMS) and periodic limb movement disorder (PLMD). Periodic limb movement disorder (PLMD) is a clinical diagnosis in which PLMS are present and have been determined to lead to either a complaint of insomnia or excessive sleepiness or to cause sleep disruption (i.e. excessive arousals) as determined by polysomnography, even though a subjective complaint may not be present (Diagnostic Classification Steering Committee [DCSC], 1990, pp. 65-68). The diagnostic criteria for PLMD (DCSC, 1990) can be briefly summarized as follows: 1) a complaint of insomnia or excessive sleepiness is present, 2) the leg movements are stereotyped and repetitive, and 3) polysomnographic monitoring shows five or more PLMs (which often cause arousals or awakenings) per hour sleep. If PLMS are present, but there is no subjective sleep complaint or objective evidence of abnormal sleep or excessive sleepiness, then the movements are generally not considered to be clinically significant and/or worthy of treatment. Finally, it is generally agreed that PLMs exert their pathological influence by causing EEG arousals and awakenings during sleep (Rosenthal et al., 1984); however, as noted earlier, the PLM arousal index may be

poorly correlated or not correlated with the average sleep latency on the MSLT (Coleman, Bliwise, et al., 1982; Mendelson, 1996).

Prevalence

Ekbom was the first to attempt to determine the prevalence of RLS in the general population (K.A. Ekbom, 1945). He questioned 503 normal individuals and 503 neurological outpatients, and found prevalence rates of 5.2 and 7.8 percent respectively. Ekbom noted that most of these were mild cases, but he did not provide any clear definition of "mild" in terms of the frequency and severity of symptoms. The value of 5.2 percent in normals is in good agreement with a recent study by O'Keeffe, Noel, and Lavan (1993) which found a prevalence rate of 4.9 percent in 307 older subjects seen at an outpatient medical clinic. In addition to these two studies, Hurry (1997) reviewed eleven additional studies which examined the prevalence of RLS in various normal or outpatient samples. The large majority of these studies found prevalence rates in the two to six percent range, although three studies found prevalences of over ten percent. When those three studies were excluded and the results were averaged across studies, the mean prevalence was found to be 4.1 percent. One general problem with these studies

was that RLS was often assessed by questionnaires (usually with only one or two items), rather than by clinical interviews. Despite this, there was general agreement across studies that the prevalence of RLS in the general population was about five percent, with most of these being mild cases.

Several prevalence studies and large case study series have found that the prevalence of RLS appears to be higher in women. For example, O'Keeffe et al. (1993) found prevalence rates of 6.3% for females and 3.0% for males. Of 237 RLS cases studied by Ekbom, 58% of the patients were women (K. A. Ekbom, 1970).

There is general agreement across a number of studies that about one-third to one-half of RLS patients report a positive family history of RLS (K. A. Ekbom, 1945; Walters, 1995; Walters et al., 1996). Several authors have presented family pedigrees that are consistent with an autosomal dominant mode of inheritance (Boghen and Peyronnard, 1976; Montagna, Coccagna, Cirignotta, and Lugaresi, 1983; Walters, Picchietti, Hening, and Lazzarini, 1990).

The age of onset appears to be variable. Ekbom found that 15% of the cases he studied first experienced symptoms before the age of 20, while the remaining cases

had their ages of onset fairly evenly distributed across the next four decades (K. A. Ekbom, 1945). Walters et al. (1996) found that 43% of 138 RLS patients they interviewed first had symptoms before the age of 20, while the remaining patients had their ages of onset fairly evenly distributed across the next four decades. Both Ekbom and Walters et al. found that periods of remission were common, and that there was a general tendency for symptoms to worsen with increasing age.

A higher than normal prevalence of RLS has been reported in a fairly large number of medical conditions and disorders. These include the following: iron deficiency (K. A. Ekbom, 1945; O'Keeffe, Noel, and Lavan, 1993), uremia (Banerji and Hurwitz, 1970; Nielsen, 1971a; Winkelman and Lazarus, 1994), rheumatoid arthritis (Reynolds, Blake, Pall, and Williams, 1986; Salih, Gray, Mills, and Webley, 1994), pregnancy (K. A. Ekbom, 1945; Goodman, Brodie, and Ayida, 1988), diabetes (Banerji and Hurwitz, 1970; Schiavi, Stimmel, Mandeli, and Rayfield, 1993), varicose veins and venous insufficiency (Kanter, 1995; Popkin, 1963), folate deficiency (Botez, 1976; Botez, Cadote, Beaulieu, Pichette, and Pison, 1976), Sjogren's syndrome (Gudbjornsson, Broman, Hetta, and Hallgreen, 1993), and as a complication following

gastrectomy (Banerji and Hurwitz, 1970; K. Ekbom, 1966). There are also case reports of individuals who developed RLS in association with various forms of peripheral neuropathy or radiculopathy (Ambrosetto and Lugaresi, 1968; Salvi et al., 1990; Walters, Hening, Wagner, and Chokroverty, 1996); however, a recent study by Rutkove, Matheson, and Logigian (1996) found that only 5.2% of 154 patients with polyneuropathy had RLS. Thus, it does not appear that patients with peripheral neuropathy have a higher than normal prevalence of RLS. Spillane (1970) reported that he had seen eight consecutive cases of RLS in a period of four years, all of whom suffered from chronic lung disease. Because this was not an unselected sample of lung disease patients, it remains unclear if patients with lung disease have a higher than normal prevalence of RLS. It is worth noting; however, that a recent prevalence study of PLMS by Ancoli-Israel et al., (1991) did find that persons with lung disease had a higher than normal prevalence of PLMS. Hurry (1997) reviewed the RLS prevalence literature in detail, and when the results were summarized across studies, the prevalence rates for RLS in the various disorders listed above were found to be as follows: iron deficiency (38%), uremia (31%), Sjogren's syndrome (24%), rheumatoid arthritis

(23%), venous insufficiency (22%), diabetes (20%), pregnancy (16%), and following gastrectomy (14%). A prevalence estimate for folate deficiency could not be derived because it was unclear if the subjects in the studies reported were unselected with respect to the presence or absence of RLS. It should also be noted that the estimates for diabetes and Sjogren's syndrome were based on data from less than 100 patients across studies, and as such, could be expected to be less reliable than the estimates of RLS prevalence in the other disorders. In recent years it has become an accepted practice to refer to the RLS that occurs in the conditions above as secondary RLS, while the terms primary or idiopathic RLS are reserved for RLS patients who do not have any of the above conditions (Walters, 1995). It should be noted that there do not appear to be any differences in symptom presentation between the primary and secondary forms (Walters, 1995).

An obvious question that arises from a review of this literature is what one factor, if any, is common to all of these conditions. Although a number of authors have pointed out that iron deficiency and/or anemia are common in several of these conditions (Pall, Williams, Fonseca, and Blake, 1987; Reynolds et al., 1986; Roger, Harris, and

Stewart, 1991), it has not been emphasized that anemia and/or circulatory problems are common in all of them. Iron deficiency is common in pregnancy (Chanarin and Rothman, 1971), in uremia patients on hemodialysis (Eschbach, Cook, Scribner, and Finch, 1977), and as a complication following gastrectomy (Lloyd and Valberg, 1977). Anemia is a well-known complication of iron deficiency (Beck, 1991a), and is also common in uremia (Beck, 1991b), rheumatoid arthritis (Cash and Sears, 1989), diabetes (Bern and Busick, 1985; Jones and Peterson, 1981), Sjogren's syndrome (Bloch, Buchanan, Wohl, and Bunim, 1965), and folate deficiency (Beck, 1991c). Circulatory problems are common in varicose veins and venous insufficiency (Goldman, Weiss, and Bergan, 1994; Ibrahim, MacPherson, and Goldhaber, 1996) and in diabetes (Colwell, 1986).

Peripheral neuropathy is also common in several of these conditions including uremia (Nielson, 1971), rheumatoid arthritis (Good, Christopher, Koepke, Bender, and Tarter, 1965), diabetes (Walker, 1986), Sjogren's syndrome (Alexander, Provost, Stevens, and Alexander, 1982), and folate deficiency (Botez et al., 1976).

The high rates of iron deficiency, anemia, and peripheral neuropathy in many of the conditions above is

important because these data are supportive of three of the four major theories of the pathogenesis of RLS. Experimentally produced iron deficiency has been shown to lead to reductions in dopamine receptor density in rats (Ashkenazi, Ben-Shachar, and Youdim, 1982). Thus, the theory that RLS is caused by dopaminergic dysfunction could account for the higher than normal prevalence of RLS seen in iron deficiency, pregnancy, hemodialysis patients, and in post-gastrectomy patients. The theory that RLS is caused by peripheral neuropathy could explain the higher than normal prevalence of RLS in uremia, rheumatoid arthritis, diabetes, Sjogren's syndrome, and folate deficiency. Finally, the theory that RLS is caused by impaired peripheral circulation (or by reduced oxygen delivery secondary to impaired peripheral circulation) could potentially account the higher than normal prevalence of RLS in all of the conditions listed above, since all of them are associated with either impaired circulation or high rates of anemia.

Unlike RLS, there are relatively few prevalence studies of PLMS in normal subjects. Only three studies with a combined total of 620 subjects have investigated this issue, and the largest of these (which included 420 subjects) used portable home recordings to assess PLMS

rather than laboratory polysomnography (Ancoli-Israel et al., 1991). These home recordings did not include measurements of EEG or other physiologic variables normally used to measure sleep; sleep was assessed using a wrist-worn actigraph. The other two large studies used laboratory polysomnography to assess PLMS. In addition to these three large studies, there are three additional studies of PLMS prevalence in various patient groups which have included small control groups of normal subjects (i.e. those either unselected for the presence or absence of sleep complaints or without any sleep complaint).

Bixler et al. (1982) were the first to investigate the prevalence of PLMS in normal subjects, and they reported a total PLMS prevalence of 11% in a sample of 100 subjects who did not have any sleep complaints. They found that the prevalence of PLMS was strongly age-related. In their sample, none of the subjects aged 18 to 29 had PLMS, only five percent of subjects aged 30 to 49 had PLMS, and 29% of subjects aged 50 to 74 had PLMS. They also found that more men (14.6%) than women (8.5%) had PLMS. Dickel and Mosko (1990) performed three consecutive nights of polysomnography on 100 subjects who were over the age of 60. These subjects were selected without any regard to the presence or absence of sleep

complaints. Using the average PLMi from all three nights for each subject, they found a total prevalence for the sample of 58%. The PLMi was significantly correlated with age, but not with sex. Ancoli-Israel et al. (1991) used portable home recordings to assess PLMS prevalence in 420 subjects over the age of 65. These subjects were also selected without any regard to the presence or absence of sleep complaints. Using a PLMi criterion of five or more, 45% of the sample had PLMS. When PLMi criteria of 10 or more and 20 or more were used, 34% and 20% (respectively) of the sample had PLMS. In the three studies with small control groups of normal subjects, Schiavi et al. (1993) found that 18% of 40 male subjects with a mean age of 52.8 years had a PLMi of 10 or greater; Ferini-Strambi et al. (1994) found that eight percent of 25 subjects (who were age-matched to a patient group with a mean age of 39.9 years) had PLMS; and Hanly and Zuberi-Khokhar (1996) found that one of nine subjects with a mean age of 65 had PLMS. Although there have been relatively few younger subjects in these six studies, there is general agreement among them that the prevalence of PLMS increases sharply in older age groups. However, studies of PLMS prevalence in patients with insomnia (in which higher than normal rates of PLMS have not been documented) have found a much more

linear increase in PLMS prevalence with increasing age, so the age of onset issue remains unresolved. Despite this, it is clear that the prevalence of PLMS is very high in older subjects.

A large number of studies have investigated the prevalence of PLMS in various medical disorders and/or patient groups. Unfortunately, only a few of these studies have included age matched control groups of normal subjects. This represents a serious shortcoming given the apparent sharp increase in PLMS prevalence in older subjects, and the small amounts of data that are actually available on PLMS prevalence in normal subjects. In addition to the lack of control groups, many of the studies discussed below arbitrarily used PLMi criteria that were different from the standard of five or more leg movements per hour. Another point worth noting is that only a few of the disorders in which a higher than normal prevalence of RLS has been documented have been investigated with respect to the prevalence of PLMS. This probably reflects the time, expense, and inconvenience involved in conducting the large scale polysomnography studies which are needed to investigate PLMS (but not RLS since RLS is not defined by polysomnographic measures).

As reviewed by Hurry (1997), there are four medical disorders in which a higher than normal prevalence of PLMS has been well established. The term "well established" was arbitrarily defined as indicating that a higher than normal PLMS prevalence (than would be expected based on the age of subjects) was found when the results were averaged across studies. An additional stipulation was that the total number of subjects included across all studies for a given disorder had to be 100 or greater. These disorders include the following: RLS (Coccagna and Lugaresi, 1981; Montplaisir et al., 1992), narcolepsy (Baker, Guilleminault, Nino-Murcia, and Dement, 1986; Mosko, Shampin, and Sassin, 1984), organic impotence (Hirshkowitz, Karacan, Arcasoy, Acik, and Williams, 1989; Schmidt, Wise, and Jackson, 1981), and uremia (Kimmel, Miller, and Mendelson, 1989; Pressman, Benz, and Peterson, 1995).

The prevalence of PLMS has been investigated in two other disorders in which the total number of subjects included across studies was greater than 100. These two disorders are insomnia and obstructive sleep apnea. As mentioned earlier, Kales et al. (1982) found the same prevalence rate of PLMS (11%) in 100 normal subjects and 200 insomnia patients. Guilleminault et al. (1975) also

reported an 11% prevalence of PLMS in 140 insomnia patients. Coleman et al. (1980) found an 18% prevalence of PLMS in 140 insomnia patients. In a large multi-center collaborative study, Coleman, Roffwarg, et al. (1982) found that 12.2% of 1,214 patients with disorders of initiating and maintaining sleep (insomnias) had either nocturnal myoclonus or RLS (the percentage of subjects with both disorders was not mentioned). Bliwise, Petta, Seidel, and Dement (1985) reported that 37% of 63 older subjects (mean age of 66 years) had PLMS. Roehrs, Zorick, Sicklesteel, Wittig, and Roth (1983) reported that 10.5% of 562 patients with sleep complaints (but without polysomnographic evidence of sleep apnea or narcolepsy) had either RLS or PLMS. The prevalence of PLMS in these patients showed a positive relationship with age: only 4.0% of patients between the ages of 20 and 40 had PLMS, while 11.4% and 21.6% of patients in the 41 to 60 and 61 and older age groups had PLMS, respectively. Coleman (1982, Figure 12.2, p. 270) presented a figure of previously published data showing the PLMS prevalence for two groups of patients (with sample sizes of 441 and 506 patients) referred for polysomnography. The data showed that PLMS prevalence increased linearly with increasing age. For example, in both groups of patients about eight

percent of the subjects in the 20 to 29 age group had PLMS, while about 20% of subjects in the 50 to 59 age group of both samples had PLMS. Overall, the results from these studies do not indicate that insomnia patients have a higher than normal prevalence of PLMS than would be expected given their age. In addition, the Roehrs et al. (1983) and Coleman (1982) data suggest that the prevalence of PLMS increases in a relatively linear fashion with increasing age, rather than showing a sharp increase in older age groups.

Several studies have reported on the prevalence of PLMS in patients with sleep apnea. Coleman et al. (1980) reported that 14% of 63 apnea patients had PLMS. In their study of PLMS prevalence in 100 older subjects who were selected without regard for the presence or absence of sleep complaints, Dickel and Mosko (1990) found that 56% of the subjects who had sleep apnea also had PLMS (defined as a PLMi of 5 or greater). This value of 56% was very similar to the 58% prevalence of PLMS for the entire sample of 100 subjects. Similarly, Ancoli-Israel et al. (1991) found that 42% of their subjects with sleep apnea had PLMS, a value that was very similar to 45% prevalence of PLMS for the entire sample of 420 subjects (subjects were selected without regard for the presence or absence

of sleep complaints). George, Ferguson, and Flaherty (1995) recently reported that 27% of 636 apnea patients with a mean age of 51.4 years had a PLMi of 10 or more. By comparison, Ancoli-Israel et al. found that 34% of their sample of 420 subjects with a mean age of 72.5 years had a PLMi of 10 or more. Overall, these studies indicate that the prevalence of PLMS in persons with sleep apnea is either very similar to or only slightly higher than its prevalence in normal individuals. One point worth repeating is that leg movements that occur at end of respiratory events in patients with sleep apnea are not counted as PLMs according to the current scoring criteria (ASDA Atlas Task Force, 1993). It is unclear whether or not this criterion was applied in the studies above.

Another interesting report with respect to sleep apnea and PLMS was a study by Fry, DiPhillipo, and Pressman (1989) which found a significant increase in PLMS when apnea patients were treated with nasal continuous positive airway pressure (CPAP). Similar results were reported by two other groups, but only for patients who had relatively severe apnea (Gokcebay, Hirshkowitz, Clay, Minhoto, and Karacan, 1993; Shaffer et al., 1993). Shaffer et al. concluded that the improved sleep continuity during CPAP treatment allowed PLMS to emerge in

those patients whose sleep had been previously severely disrupted by sleep apnea. In contrast to these findings, George et al. (1995) reported only 18% of 174 apnea patients with PLMS had an increase in their PLMi during CPAP treatment (82% had a decrease in their PLMi). These later results, which were based on a very large sample, indicated that CPAP tended to improve rather than exacerbate PLMS.

A higher than normal (or high) prevalence of PLMS has been reported in nine additional medical disorders, in which the total number of subjects included across studies was less than 50. Because of the small number of subjects studied with each of these disorders, these results should probably be viewed as preliminary findings. As such, the disorders will only be mentioned here. These nine disorders include the following: congestive heart failure (Hanly and Zuberi-Khokhar, 1996), diabetes (Schiavi et al., 1993), multiple sclerosis (Ferini-Strambi et al., 1994; Potolicchio, Calderon, and Richert, 1991), fibrositis syndrome (Moldofsky, Tullis, and Lue, 1986), chronic fatigue syndrome (Morehouse, MacDonald, Haase, Marrie, and Braha, 1994), leukemia (Kotagal et al., 1985), coma (Oskenberg, 1989), neuroleptic-induced akathisia (Walters, Hening, Rubinstein, and Chokroverty, 1991), and

in family members of children with hereditary progressive dystonia (Gadoth, Costeff, Harel, and Lavie, 1989). There are also case reports of PLMS in patients with spinal cord injury (Dickel, Renfrow, Moore, and Berry, 1994; Yokota, Hirose, Tanabe, and Tsukagoshi, 1991) and head injury (Budha, 1996).

Unlike RLS, there is no one factor or pathology common to all of these conditions, although anemia and/or circulatory problems are common in several of them (leukemia, uremia, diabetes, impotence, and congestive heart failure), and abnormalities of dopamine or dopamine receptors have been reported (or postulated) in hereditary progressive dystonia (Segawa, Ohmi, and Itoh, 1971), neuroleptic-induced akathisia (Sachdev, 1995), and impotence (Lal et al., 1989). One general aspect of several of the remaining conditions (narcolepsy, multiple sclerosis, and coma) is that they are disorders in which a major pathology of the central nervous system is involved.

Pathophysiological Findings

Most studies of RLS based on large case study series of patients are in agreement that physical and neurological examinations are usually normal in idiopathic RLS patients (K. A. Ekbom, 1945; Gorman et al., 1965; Morgan, 1967; Walters and Hening, 1987). The neurological

examination may be abnormal if the patient has diabetes, uremia, or rheumatoid arthritis (Gorman et al., 1965; Nielsen, 1971a, Salih et al., 1994), but such cases would be considered secondary, rather than idiopathic, RLS. The physical and neurological examinations are also usually normal in PLMS patients (Coleman et al., 1980; Guilleminault et al., 1975), although a recent study by McCall, Edinger, and Lininger (1991) found that nine of 17 PLMS patients (53%) had one or more neurological abnormalities. Unfortunately, the percentage of these patients with diabetes, uremia, or other conditions that might have led to these abnormal findings was not reported.

Many studies of RLS patients have reported that a significant number of them (up to 20% to 30%) have iron deficiency (K. A. Ekbom, 1960; Norlander, 1953; O'Keeffe, Gavin, and Lavan, 1994; Parrow and Werner, 1966), although other authors have reported only isolated cases in their samples (Gorman et al., 1965; Morgan, 1967; Young et al., 1969). A recent study by Baran, Goldberg, DiPhillipo, Curran, and Fry (1996) found that three of 20 PLMS patients had low ferritin levels. Some studies have found elevated blood urea nitrogen values suggestive of uremia in PLMS patients (Bliwise, Petta, Siedel, and Dement,

1985; Coleman et al., 1980). Because RLS may be associated with iron deficiency or other anemias, diabetes, and uremia, it is generally recommended that laboratory tests for these conditions be done whenever a patient presents with RLS (Montplaisir et al., 1994). However, the question of what percentage of RLS patients have secondary versus idiopathic RLS (or PLMS) is not a well-investigated issue. The only data pertinent to this question are from the prevalence study by O'Keeffe et al. (1993). They found that 15 of 307 patients seen at a geriatric outpatient care facility had RLS. Eight of these 15 patients (53%) had conditions that are known to be associated with RLS (4 had iron deficiency anemia, and 2 had diabetes, and 2 had chronic lung disease).

The theory that RLS (and PLMS) is caused by peripheral neuropathy has been popular over the years, and a large number of neurophysiological studies in RLS and PLMS patients have been reported. A total of eight such studies in idiopathic or unselected RLS patients and four in PLMS patients have been reported. Each of these will be briefly discussed below.

Gorman et al. (1965) briefly mentioned that electromyogram (EMG) studies were performed in 11 RLS patients, and found to be abnormal in only two of these

patients. In both cases, the abnormalities were thought to be secondary to diabetes. Coccagna and Lugaresi (1981) briefly mentioned in a review paper that they found positive Babinski signs and delayed nerve conduction time in their RLS patients in the evening when symptoms were present, and in addition, they found that these signs were reduced or absent the following morning. It was unclear from their paper how many subjects they actually studied, and what percentage of them had abnormal findings. Guilleminault and Flagg (1984) mentioned that EMGs and nerve conduction studies were normal in the five PLMS patients they studied. Mosko and Nudleman (1986) found no differences in auditory and somatosensory evoked potentials between a group of ten RLS/PLMS patients and ten normal controls. Wechsler, Stakes, Shahani, and Busis (1986) performed nerve conduction, EMG, evoked potential, and reflex studies in six PLMS patients. The nerve conduction, EMG, and evoked potential studies were normal in all cases, but two patients had abnormal H-reflexes and all six had abnormal blink reflexes (consisting of additional long latency components). Wechsler et al. concluded that these findings were indicative of increased excitability of brainstem and spinal reflexes. Akpinar (1987) briefly mentioned that neurological examinations,

EEGs, and EMGs were normal in 16 RLS patients he studied. Martinelli, Coccagna, and Lugaresi (1987) found abnormal H-reflexes and other reflexes in three of six RLS/PLMS patients they studied. Zucconi et al. (1989) performed neurological examinations and sensory and motor nerve conduction studies on nine RLS patients, and found that only one patient had abnormal findings (which were suggestive of Parkinson's disease). Bliwise, Ingham, Date, and Dement (1989) performed sensory and motor nerve conduction studies in both upper and lower extremities of 24 elderly PLMS patients. Although no control group was used, the values obtained were stated to be within the normal range for the age group of the subjects. Smith et al. (1992) used central magnetic stimulation to study motor nerve conduction in four RLS patients and nine PLMS patients. There were no differences in conduction times between these subjects and normal controls. Montplaisir, Lapierre, and LaVigne (1994) performed spectral analyses of EEGs that were recorded during the evening when symptoms were present in RLS patients, and reported that there was periodic slowing that was correlated with waking leg movements in these subjects. They concluded that this slowing was indicative of drowsiness, and postulated that leg movements in both RLS and PLMS required a critical

level of cortical arousal to appear. Iannaccone et al. (1995) performed neurological examinations, sensory and motor nerve conduction studies, EMGs, and temperature perception tests in eight patients with primary RLS. The neurological examinations and nerve conduction studies were normal in all patients, but five of them had abnormal EMGs and seven had impaired temperature perception test results.

Overall, the large majority of the patients in these twelve studies had no abnormal electrophysiological findings. Thus, there is little support for the idea that RLS (or PLMS) is caused by peripheral neuropathy. The abnormal reflex findings (Coccagna and Lugaresi, 1981; Martinelli et al., 1986; Wechsler et al., 1986) are probably the most consistent across studies. The report by Coccagna and Lugaresi (1981) that abnormalities were seen primarily during symptom presentation is also very interesting, but unfortunately, there has not been any attempt to replicate those results.

Four studies have investigated the prevalence of neurophysiological abnormalities in patients with secondary RLS (three studies with uremic RLS patients, one in RLS patients with rheumatoid arthritis). Because peripheral neuropathy is known to occur in both uremia and

rheumatoid arthritis (Good et al., 1965; Nielsen, 1971a), it is not surprising that some RLS patients with uremia or rheumatoid arthritis have peripheral neuropathy. What is of interest is the question of whether or not peripheral neuropathy occurs in more commonly in the uremic and arthritis patients who do have RLS than in those who do not. Callaghan (1966) was the first author to suggest that RLS could be caused by peripheral neuropathy. In his 1966 study, he reported that five patients who had RLS secondary to uremia all had either clinical or neurophysiological evidence of peripheral neuropathy. However, he did not include any non-RLS patients in his study. Nielsen (1971b) studied 109 patients with uremia, and found no relationship between the presence or absence of RLS and clinical signs suggestive of peripheral neuropathy (i.e. peripheral neuropathy was equally common in RLS and non-RLS patients). Similar results were reported by Roger et al. (1991) in 55 uremic patients who were receiving either renal or peritoneal dialysis. Salih et al. (1994) performed sensory and motor nerve conduction studies and somatosensory evoked potentials on 14 rheumatoid arthritis patients with RLS and nine rheumatoid arthritis patients without RLS. Ten of the 14 RLS patients (71%) had abnormal studies while only three of

nine non-RLS patients (33%) had abnormal findings. However, there was clinical and laboratory data which suggested that the RLS group had more severe arthritis than the non-RLS group, so the groups were not equated for disease severity. Taken together, the results from these last three studies do not provide convincing evidence that secondary RLS is caused by peripheral neuropathy.

Two studies have used muscle and/or nerve biopsies to further investigate the possibility of neuropathy or myopathy in RLS patients. Harriman, Taverner, and Woolf (1970) examined biopsies of the peroneus brevis muscle (and associated nerve endings) in ten patients diagnosed with RLS. Although a number of abnormalities were found (e.g. excessive axonal sprouting, end-plate abnormalities, spherical axonal swellings), these were seen with equal frequency in an age-matched control group. Iannaccone et al. (1995) examined sural nerve biopsies in eight patients with primary RLS. The RLS biopsies showed significantly lower myelinated fiber density and more evidence of axonal atrophy and myelin alterations than biopsies from age-matched controls. Despite these abnormal findings, it should be noted that the sensory and motor nerve conduction studies in these subjects were normal.

Two studies have used neuroradiological techniques to investigate possible CNS abnormalities in RLS/PLMS patients. Staedt et al. (1995a) used single photon emission computed tomography to investigate striatal D2 dopamine receptor density in 20 RLS/PLMS patients (14 with RLS, 6 with only PLMS) and 10 age matched controls. A ratio of basal ganglia to cortical tracer uptake was used as the dependent variable. The actual values of tracer uptake in the cortex and basal ganglia were not presented; only the ratio was used. The value for the patients (1.40) was about nine percent lower than the value for the controls (1.53), a difference that was statistically significant. Both values indicate that dopamine receptor density is higher in the basal ganglia, while the lower value for the RLS/PLMS group indicates that their basal ganglia dopamine receptor density was lower than that of the controls. In a follow-up study on four patients who were treated with L-Dopa, an unexpected up-regulation in striatal dopamine receptor density was found (Staedt et al., 1995b). Staedt et al. suggested that this might indicate a dysfunction in the corticostriatal input to the basal ganglia. Walters et al. (1995) used positron emission tomography to investigate global and regional brain glucose metabolism in five RLS patients and 20

normal controls. There were no significant differences between the groups.

A number of authors have noted that RLS and PLMS patients often complain of cold feet (Ancoli-Israel et al., 1986; K. A. Ekbom, 1945; Ware et al., 1988). Ware et al. performed photoplethysmographic examinations of peripheral blood flow in two RLS patients who complained of cold feet, and found evidence suggestive of excessive peripheral vasoconstriction in both of these patients. Similar examinations on their next ten PLMS patients found that four of these subjects also had evidence of excessive peripheral vasoconstriction. Ware et al. suggested that this excessive vascular tone was caused by excessive sympathetic nervous system activity. Unfortunately, no control group was included in this study, so it remains unclear if RLS/PLMS patients are more likely to have impaired peripheral circulation than normal controls.

In summary, there are few pathophysiological findings in the majority of patients with both RLS and PLMS. Some RLS patients do have anemia, uremia, diabetes, and associated peripheral neuropathy, and such secondary RLS cases may represent a significant percentage of total RLS cases. Most other abnormal findings which have been

reported have not yet been replicated, and there is obviously much work that remains to be done in this area.

Treatment

A large variety of drugs have been used to treat RLS and PLMS over the years. Ekbom was the first to attempt treatment of RLS (K. A. Ekbom, 1944, 1945). Based on his theory that RLS was caused by impaired peripheral circulation, Ekbom administered the vasodilators carbachol (an acetylcholine agonist) and tolazoline (an alpha adrenergic blocker) to a large number of RLS patients, and he reported that about two thirds of his patients had an improvement in their symptoms with each of these drugs (K. A. Ekbom, 1945). Ekbom defined "improvement" as a report from the patient that "the symptoms occurred so seldom or in such a mild degree that the patient no longer bothered much about them." (K. A. Ekbom, 1945; p. 51). However, other investigators found that only small percentages of patients improved with either carbachol (Brenning, 1971) or tolazoline (Parrow and Werner, 1966). Norlander (1953) found that injections of iron-dextran had a beneficial effect on RLS symptoms even in patients who were not iron deficient. This led him to suspect that the dextran component of the iron-dextran injections was exerting a therapeutic effect. When he used dextran alone in three

patients, two of the three had an improvement in their RLS symptoms. In one of the two patients who improved, there was a complete remission of symptoms, while in the other, symptoms remitted only for one day. Parrow and Werner (1966; p. 402) later reported that 55 of 64 RLS patients (86%) they treated with dextran injections became completely symptom free, while an additional four patients "improved but were not completely free from symptoms". This improvement often lasted weeks or months. Dextran is a high molecular weight branched polysaccharide which is used clinically as a plasma volume expander in patients who have lost large amounts of blood (Mattox et al., 1991). Because it expands plasma volume, the hematocrit is lowered; this lowers the blood viscosity and improves blood flow in the microcirculation (Kreimeier, Brucker, Niemczyk, and Messmer, 1990). Because the plasma half life of dextran is only about 15 hours, the mechanism by which it might have acted to produce the long-lasting relief of symptoms reported by Parrow and Werner is not evident. Kanter (1995) recently reported that sclerotherapy treatment of varicose veins had the unexpected beneficial side effect of producing dramatic relief from RLS symptoms in 111 of 113 varicose vein patients who also had RLS. Relief was defined in this

study by a patient report of "either complete resolution or sustained marked improvement of symptoms" (Kanter, 1995; p. 329). Sclerotherapy is a technique in which a sclerosing agent (usually sodium tetradecyl sulphate) is injected into a varicose vein after it has been occluded. The vessels eventually undergo complete fibrosis and reabsorption, with a resulting improvement in peripheral venous circulation. This improvement in peripheral circulation was the apparent mechanism by which sclerotherapy improved RLS symptoms. Recently, a number of studies have shown that the anti-hypertensive agent clonidine has a beneficial effect on RLS symptoms (Bastani and Westervelt, 1987; Handwerker and Palmer, 1985; Steiner, 1987; Wagner et al., 1996), although in the one study in which polysomnography was performed, no reduction in PLMs was observed (Wagner et al., 1996). Clonidine is an alpha-2 adrenergic agonist which is believed to reduce total peripheral vascular resistance by acting on central adrenergic autoreceptors (Hoffman and Lefkowitz, 1990). It may also have a direct peripheral vasodilatory effect (Shaw, Hunyor, and Korner, 1971). Unfortunately, side effects such as sedation and dry mouth are common with clonidine (Hoffman and Lefkowitz, 1990). Such side effects were noted by both Bastani and Westervelt (1987)

and Wagner et al. (1996), and were severe enough to necessitate cessation of therapy in three of six patients in the Bastani and Westervelt study and in three of seven "responders" in the Wagner et al. study. These side effects may limit the clinical usefulness of clonidine in treating RLS. Despite this, the results of the above studies, when taken together, suggest that drugs which exert a vasodilatory effect or which improve circulation have a beneficial effect on RLS symptoms.

Several studies over the years have noted that correction of anemia and iron or folate deficiency are effective in relieving RLS symptoms. Norlander (1953) found that blood transfusions to correct anemia were effective in all six RLS patients to whom they were administered. Both Norlander (1953) and Parrow and Werner (1966) found injections of iron-dextran to be effective in treating RLS patients; although, as noted above, this effect may have been partially mediated by the dextran component of the iron-dextran injections. However, both Norlander (1953) and O'Keeffe et al. (1993) also found that oral iron supplementation was effective in relieving RLS symptoms. Finally, Botez and his colleagues found folate supplements to be effective in treating RLS symptoms in patients who were folate deficient (Botez,

1976; Botez et al., 1976). These studies are consistent in finding that correction of anemia and related deficiency states is effective in treating RLS, and they further suggest a causative role for anemia in the pathogenesis of some RLS cases.

Ekbom noted in his 1945 monograph that several of his RLS patients had discovered on their own that opioids were very effective in relieving RLS symptoms. This observation was subsequently confirmed by a number of investigators in both open (Akpinar, 1982; Hening et al., 1986; Trzepacz, Violette, and Sateia, 1984) and placebo controlled trials (Walters et al., 1993). For example, all five RLS patients studied by Akpinar (1982) and all three patients studied by Trzepacz et al. (1984) were reported to have improved with opioid treatment (in both studies "improvement" was assessed by patient report and/or clinical interviews; objective measures of RLS symptomatology were not obtained). Four of five patients studied by Hening et al. had decreases in waking leg movements of 65% or more. In the placebo controlled study conducted by Walters et al. (1993), rating scales were used to assess waking leg sensations and motor restlessness. Both variables decreased significantly during the treatment period. An examination of the data

presented for individual subjects showed that six of ten subjects had a 70% or more decrease in their ratings of leg sensations while five of ten had similar decreases in their ratings of motor restlessness. The effect of opioids on PLMS appears to be less pronounced. Walters et al. (1993) found a 53% decrease in the PLMi from baseline with oxycodone, while Kaplan, Allen, Buchholz, and Walters (1993) reported a 35.4% decrease in the PLMi from placebo with propoxyphene (this decrease was not statistically significant). Kavey, Walters, Hening, and Guidro-Frank (1988) used a variety of opioids in four PLMS patients, and found that two patients had their leg movements almost completely eliminated while there was no effect in the other two. The clinical use of opioids in RLS and PLMS patients is also limited by concerns about the possible development of tolerance, dependence, and abuse (Montplaisir et al., 1992).

A fairly large number of benzodiazepines have been used to treat both RLS and PLMS. Several early open trials found that diazepam was effective in treating RLS (K. A. Ekbom, 1970; Morgan, 1967; Spillane, 1970). Matthews (1979) was the first to report that clonazepam was beneficial in treating RLS patients. The efficacy of clonazepam in treating both RLS and PLMS has subsequently

been shown in a large number of studies (see Hurry, 1997, for a detailed review), including double-blind placebo controlled studies (Montagna, de Bianchi, Zucconi, Cirignotta, and Lugaresi, 1984; Peled and Lavie, 1987). In the three studies in which clonazepam was used to treat PLMS, decreases in the PLMi of 34% (Mitler, Browman, Menn, Gujavarty, and Timms, 1986), 65% (Ohanna, Peled, Rubin, Zomer, and Lavie, 1985), and 43% (Peled and Lavie, 1987) have been reported. Scharf, Brown, and Hirschowitz (1986) reported that alprazolam was effective in treating eight of ten RLS patients in an open trial. Moldofsky, Tullis, Quance, and Lue (1986) found that nitrazepam produced a 65% decrease in the PLMi of 13 PLMS patients they treated. Mitler et al. (1986) found that temazepam improved sleep quality but did not decrease the PLMi in ten PLMS patients they treated. Similar results (i.e. improved sleep quality but no decrease in PLMs) have been reported for triazolam in three studies (Bonnet and Arand, 1990, 1991; Doghramji, Browman, Gaddy, and Walsh, 1991). In summary, several benzodiazepines, including alprazolam, diazepam, clonazepam, and nitrazepam have been found to be beneficial in treating RLS and PLMS. Clonazepam is currently regarded as the treatment of choice for younger and less severely affected RLS/PLMS patients, although it

is contraindicated in cases where there is a comorbid sleep-related respiratory disorder (Montplaisir et al., 1992).

Akpinar (1982) was the first to report that L-DOPA was effective in treating RLS symptoms. Because his results were published in a letter to the editor, they apparently went unnoticed for several years. Montplaisir and his colleagues independently discovered the effectiveness of L-DOPA in treating RLS several years later (Montplaisir, Godbout, Poirier, and Bedard, 1986). Since these two initial studies, a large number of studies have been published in which L-DOPA has been used to treat both RLS and PLMS. These have included both open trials (e.g. Akpinar, 1987), and double-blind placebo controlled studies (e.g. Boivin, Montplaisir, and Poirier, 1989; Brodeur, Montplaisir, Godbout, and Marinier, 1988; Kaplan et al, 1993). There is almost uniform agreement across these studies that L-DOPA is very effective in treating RLS and PLMS, although it is interesting to note that PLMs are usually not completely eliminated (see Hurry, 1997, for a detailed review). The dopamine agonist bromocriptine has also been found to be effective in treating both RLS (Akpinar, 1982; Walters, Hening, Kavey, and Chokroverty, 1988) and PLMS (Boivin, Lorrain, and

Montplaisir, 1993). Several studies have noted that a morning rebound or evening augmentation of RLS symptoms may occur with L-DOPA treatment in some RLS patients (Allen and Early, 1996b; Becker, Jamieson, and Brown, 1993; Guilleminault, Cetel, and Philip, 1993). Despite this, L-DOPA is clearly effective in treating both RLS and PLMS, and it is currently regarded as the treatment of choice for older and more severely affected RLS/PLMS patients (Montplaisir et al., 1992).

Several studies have found that anti-convulsants may be beneficial in treating RLS. Hogg (1972) reported that phenytoin was effective in relieving RLS symptoms in seven of his RLS patients. Carbamezapine was later reported to be effective in treating RLS in three studies, two of which were double-blind placebo controlled trials (Lundvall, Abom, and Holm, 1983; Telstad et al., 1984; Zucconi et al, 1989), although in the one study in which nocturnal leg movements were recorded (Zucconi et al., 1989), PLMs were not affected. More recently, gabapentin has been reported to be effective in treating RLS in two open trials (Cochran and Williams, 1996; Mellick and Mellick, 1996). These results were not replicated in a third study (Allen and Early, 1996a) which found that only 5 of 11 RLS patients had any improvement with gabapentin.

In summary, vasodilators, correction of anemia, opioids, benzodiazepines, dopamine agonists, and anti-convulsants have all been reported to be effective in treating either RLS, PLMS, or both conditions. As mentioned earlier, clonazepam and L-DOPA are currently regarded as the treatments of choice. Problems such as drug tolerance and morning rebound and evening augmentation of symptoms are currently being managed by rotating patients to a different drug every few months, or more often, as needed (Allen and Early, 1996b).

Pathogenesis

Over the years many authors have speculated about the pathogenesis of RLS and PLMS, but only four theories of RLS and two of PLMS have been discussed with some frequency. These include the following for RLS: reduced peripheral blood flow, peripheral neuropathy, opioid dysfunction, and dopaminergic dysfunction. The two major theories of PLMS include oscillations of reticular system excitability and the spontaneous Babinski response theory. In addition to these theories, it should be noted that before it became widely known that PLMS occurred in most RLS patients, a fairly large number of authors suggested that RLS was psychogenic in origin (e.g. Gorman et al., 1965; Morgan, 1967; Spillane, 1970; Young et al., 1969).

Ekbom was the first to speculate on the pathogenesis of RLS (K. A. Ekbom, 1944, 1945), and based on several lines of evidence, he proposed that RLS was caused by a buildup of toxic metabolites in the lower limbs secondary to reduced peripheral blood flow. Evidence that he cited in favor of this theory was as follows: the symptoms were relieved by drugs which had a peripheral vasodilatory effect, many patients complained of cold feet, the symptoms seemed to be caused by prolonged exposure to cold in several patients, and the symptoms resembled acroparesthesia, an upper limb paresthesia which was thought to be vascular in origin. Ekbom (1945) also pointed out that RLS symptoms were intermittent rather continuous; continuous symptoms would have suggested a physical lesion, whereas intermittent symptoms were consistent with a transient ischemia-induced paresthesia. In his later reviews (K. A. Ekbom, 1960, 1970), Ekbom also noted that anemia and iron deficiency exercerbated the symptoms of RLS. In fact, as noted earlier, most of the medical conditions in which a higher than normal prevalence of RLS and PLMS has been demonstrated are associated with either anemia or impaired circulation. Like Ekbom, other researchers have also reported that many RLS (and PLMS) patients complain of cold feet (Ancoli-

Israel et al., 1986; Ware et al., 1988). Ware et al. also found direct evidence of reduced peripheral blood flow in two of two RLS patients and four of ten PLMS patients. Ware et al. suggested that excessive sympathetic nervous system activity might have caused this excessive vascular tone. They also suggested that oscillations of sympathetic nervous system activity might underlie the periodicity of PLMS, and cited a number of studies (primarily those on Mayer waves of peripheral blood pressure) in which a 20 to 40 second periodicity of sympathetic activity had been demonstrated. Finally, in their recent clonidine treatment study of RLS, Wagner et al. (1996) proposed that clonidine exerted its therapeutic effect by improving peripheral blood flow.

Callaghan (1966) was the first to suggest that RLS might be caused by peripheral neuropathy. This theory has been popular over the years, and despite the overall lack of support for it, the occasional positive finding (e.g. Iannaccone et al, 1996; Wechsler et al., 1986) seems to have kept it alive. The high prevalence of peripheral neuropathy in several conditions in which RLS is common (e.g. uremia, rheumatoid arthritis, diabetes) is additional evidence in support of this theory, although as noted earlier, RLS is seen with the same frequency in

uremic patients with and without peripheral neuropathy (Nielsen, 1971b).

Studies which have shown opioids to be effective in treating RLS have led to the theory that RLS might be caused by some dysfunction in the endogenous opioid system (Hening et al., 1986; Walters, Hening, Cote, and Fahn, 1986). Walters et al. (1986) have specifically suggested that the mu opioid receptor might be involved in RLS, since all of the drugs which have been shown to be effective in treating RLS are mu agonists. Apart from the treatment data, there is essentially no other evidence which supports this theory.

The finding that L-DOPA was very effective in treating RLS led to the theory that RLS is caused by a dopaminergic dysfunction. As reviewed earlier, there is substantial evidence that dopamine agonists are very effective in treating both RLS and PLMS. Also noted earlier was the study of Staedt et al. (1995a) which found direct evidence of reduced dopamine receptor density in the basal ganglia of RLS and PLMS patients. The finding that iron deficiency can cause reductions in dopamine receptor density (Ashkenazi et al.,1982) coupled with the high prevalence of iron deficiency in many conditions in which RLS is common (pregnancy, hemodialysis, gastrectomy)

is further evidence in support of the dopamine theory. Finally, several authors have pointed out RLS has many similarities to neuroleptic induced akathisia (NIA), a disorder which is seen as a side effect of dopamine blocking neuroleptic medications (Blom and Ekbom, 1961; Walters et al., 1991).

In one of the earliest descriptions of PLMS in RLS patients, Behrman (1958) suggested that these symptoms were "a manifestation of a raised excitatory state referable to bulbar reticular activity". In their 1968 review paper, Lugaresi et al. (1968) agreed with Behrman that both RLS and PLMS might be caused by abnormal activity in the brainstem reticular formation. They specifically suggested that RLS and PLMS might result from "rhythmical fluctuations of reticular excitability" which in turn might be caused by periodic oscillations in blood flow (i.e. Mayer waves) to the brainstem. In a later study Lugaresi, Coccagna, Mantovani, and LeBrun (1972) showed that several periodic phenomena in sleep (PLMs, apneic events in persons with sleep apnea, Mayer waves of systemic blood pressure in normal subjects) all had similar periodicities of 20 to 30 seconds. They suggested that all of these phenomena might be caused by oscillations of reticular excitability, and again

suggested that the oscillations of reticular tone might be due to periodic oscillations in blood flow or to oscillations in pH, O_2, and CO_2 secondary to these blood flow changes. Unfortunately, Lugaresi and colleagues never did measure systemic blood pressure or reticular activity in PLMS patients, so direct confirmation of this theory is lacking. Despite this, the idea that a brainstem oscillator mediates the periodicity of PLMs has been generally well accepted over the years.

Smith (1985) proposed that PLMs were spontaneously occurring Babinski responses. He based this idea on videotaped analyses of PLMs which showed that they did in fact appear to be similar to Babinski responses. The Babinski response is an abnormal reflex which is seen following damage to the pyramidal tracts (van Gijn, 1995). It is thought to be inhibited in normal individuals by descending inhibition from the pyramidal tracts. In support of Smith's idea that there is a reduction in this descending inhibition during NREM sleep, two studies have shown that the Babinski response can be elicited during NREM (but not REM) sleep in normal individuals (Batini, Fressy, and Gastaut, 1964; Fujiki, Shimizu, Yamada, Yamamoto, and Kaneko, 1971). The absence of PLMs (and Babinski responses) during REM sleep may both be

attributable to the generalized muscle atonia seen in this sleep stage. This atonia has been shown to be mediated by the nucleus reticularis gigantocellularis, a medullary reticular nucleus which projects to all levels of the spinal cord (Kanamori, Sakai, and Jouvet, 1980). Apart from his observation that PLMs appear to be spontaneously occurring Babinski responses, Smith has offered little additional explanation of how such responses might occur spontaneously, why they occur in some individuals but not others, and how they might be linked to RLS symptoms. Thus, this theory represents primarily an explanation for what PLMs are, rather than why they occur.

Critique of Pathogenic Theories

There are several major problems with the pathogenic theories of RLS and PLMS discussed above. The first and most important of these is the small number of studies which have directly investigated the main tenets of the theories discussed above (the peripheral neuropathy theory of RLS is the one exception to this). For example, there have been no studies attempting to determine if there are opioid receptor abnormalities in RLS/PLMS patients, and only one such study investigating (D2) dopamine receptor distributions in RLS/PLMS patients. The only study investigating peripheral blood flow in RLS and PLMS

patients included only two RLS patients and did not have a control group of normal subjects. There has been no attempt to determine if Mayer waves, sympathetic nervous system activity, or reticular system activity are correlated with (and time-locked with) periodic leg movements. There also has not been any attempt to determine if RLS/PLMS patients are more likely to show elicited Babinski responses during NREM sleep than normal controls. The eventual acceptance or rejection of the theories above can only be based on such direct investigation, and there is clearly much work that remains to be done in this regard.

Another problem with these theories is that they are vague and poorly developed. For example, there has been no attempt to suggest which peripheral nerves might be most likely to be involved in producing RLS symptoms, if RLS is indeed due to peripheral neuropathy. There also has been no suggestion of which brain or spinal cord areas rich in opioid receptors might be responsible for producing RLS. Similarly, there has been little discussion of which dopaminergic projections within the CNS might be involved in RLS/PLMS. In general, the pathogenic theories of RLS and PLMS consist primarily of unelaborated statements and proposals, such as the idea

that RLS is due to an opioid (or dopaminergic) dysfunction.

A related problem is that there has been no attempt on the part of the proponents of the theories listed above to explain all of the well-established features of either RLS or PLMS in terms of their theories. Instead, most authors have emphasized only those features of the disorder that they can explain in terms of their theories. Hurry (1997) suggested that there are at least seven unique and well established features of RLS and PLMS that any pathogenic theory of the two disorders should be able to (or attempt to) explain. These seven features are: (1) the restriction of RLS paresthesias to the lower legs excluding the feet; (2) the precipitation of RLS symptoms by inactivity; (3) the relief of RLS symptoms by movement; (4) the circadian (and/or sleep-related) appearence of symptoms in RLS and PLMS; (5) the higher than normal prevalence of RLS and PLMS in the various disorders reviewed above; (6) the reason for the effectiveness of the various drugs that have been shown to be beneficial in treating RLS and PLMS; and (7) the mechanism responsible for the periodicity of PLMs. In addition, any theory of either RLS or PLMS should be able to explain the strong tendency of the two disorders to occur together. Below,

each of the major pathogenic theories of RLS and PLMS will be considered with respect to how well it appears to be able to explain all of these features. Only brief comment will be made on Smith's spontaneous Babinski response theory, since, as noted earlier, it is primarily an explanation of what PLMs are rather than why they occur and how they are related to RLS.

The reduced peripheral blood flow theory (and the related suggestion of excessive sympathetic tone; Ware et al., 1984) can potentially explain many of the features of RLS and PLMS, but the restriction of sensory symptoms to the lower legs excluding the feet represents a very difficult issue for this theory. If RLS is in fact caused by reduced blood flow to the lower legs, then it is very difficult to understand why the paresthesias in RLS are not generally seen in the feet. The reduced peripheral blood flow theory would presumably suggest that they should be most common in the feet because all of the major arteries which supply blood to the lower legs also supply the feet (see Moore, 1985, Figure 4-31, p. 432), and if blood flow is reduced in general, then the most distal areas supplied by a given artery should be affected the most. The precipitation of RLS symptoms with inactivity and their relief with movement are potentially explainable

in terms of this theory, since a number of studies have shown that blood flow to legs is substantially less while an individual is at rest than while he or she is engaging in even mild or moderate exercise (Hinsenkamp, d'Hollander, Coussaert, Rasquin, and Schoutens, 1980; Lassen and Kampp, 1965). Similarly, this theory can potentially explain the circadian variation in RLS/PLMS symptoms, since there are well known reductions in heart rate, blood pressure, and peripheral blood flow during the evening and during non-REM sleep (Kanecko, Zechman, and Smith, 1968; Littler, Honour, Carter, and Sleight, 1975; Millar-Craig, Bishop, and Raftery, 1978; Synder, Hobson, Morrison, and Goldfrank, 1964). As noted earlier, anemia and/or impaired circulation are common to the large majority of medical conditions in which there is a higher than normal prevalence of RLS and PLMS, so the reduced peripheral blood flow theory can potentially account for much of these data as well. Although some of the treatment data can be explained in terms of the reduced peripheral blood flow theory (e.g. correction of anemia, vasodilators), some of these data are more difficult to explain. This includes the beneficial effects of opioids, benzodiazepines, and anticonvulsants. It is apparently not well known among RLS researchers that dopamine

agonists have been shown to increase both peripheral and cerebral blood flow (Bogaert and De Schaepdryver, 1967; Edvinsson, MacKenzie, and McCulloch, 1993, p. 245). Finally, the periodicity of PLMs is also potentially explainable in terms of the reduced peripheral blood flow theory. Both Ware et al. (1988) and Lugaresi et al. (1972) suggested that the 20 to 40 second oscillations in systemic blood pressure known as Mayer waves might underlie this periodicity. Although neither author gave a detailed proposal of how Mayer waves might actually cause PLMs, these oscillations are one of the few physiologic phenomena that are known to have the same period (i.e. 20 to 40 seconds) as PLMs. In summary, the reduced peripheral blood flow theory of RLS and PLMS can potentially explain most of the well established features of both disorders. Its main shortcomings are its apparent inability to explain the anatomic distribution of paresthesias in RLS and its inability to explain some treatment data.

As reviewed above, there have been a large number of studies attempting to demonstrate peripheral neuropathy in RLS and PLMS patients; however, most of these studies have failed to document such pathology in the large majority of RLS and PLMS patients. In addition to this lack of direct

evidence, the peripheral neuropathy of RLS also has difficulty in explaining many of the well established features of RLS and PLMS. The anatomic distribution of paresthesias in RLS is the first of these. A careful review of the dermatomes supplied by the nerve roots at various spinal cord segments, and of the cutaneous areas of the legs supplied by individual peripheral nerves, shows that none of these areas match the areas on the lower legs where the paresthesias in RLS typically occur (see Carpenter and Sutin, 1983, pp 190-191 for a review of dermatomes and peripheral nerve distributions). The intermittent nature of RLS symptoms (i.e. their appearance at rest, their relief with movement, and their circadian variation) are also difficult to explain in terms of the peripheral neuropathy theory, since peripheral neuropathy generally produces persistent rather than intermittent symptoms (Thomas, 1984). A similar argument could apply to the periodic nature of PLMS. As noted earlier, some of the conditions in which a higher than normal prevalence of RLS and PLMS occur do have peripheral neuropathy as an associated feature (e.g. uremia, rheumatoid arthritis, diabetes), so the peripheral neuropathy theory of RLS could potentially account for some of this data. However, many of those conditions are not associated with

peripheral neuropathy, and as reviewed earlier, many RLS patients with uremia, rheumatoid arthritis, and diabetes do not have any evidence of peripheral neuropathy. The treatment data are also difficult to understand in terms of the peripheral neuropathy theory, since the standard therapy for peripheral neuropathy consists of treating the underlying condition which caused it, and utilizing various forms of physical therapy to overcome its residual effects (Stillwell, 1984). In summary, not only does the peripheral neuropathy theory of RLS have little empirical support, but it is also apparently unable to explain most of the well established features of RLS and PLMS.

As reviewed above, the opioid theory is based solely on the treatment data which has shown opioids, and mu agonists in particular, to be effective in treating RLS. The putative opioid dysfunction in RLS could consist of decreased levels of endogenous opioids, decreased levels of opioid receptors, or some combination of these factors. In attempting to explain the anatomical distribution of the paresthesias in RLS in terms of the opioid theory, it is first necessary to review which CNS areas mediate somatosensation in the lower legs. Because there is clinical evidence that several sensory modalities may be involved in the paresthesia of RLS (e.g. deep tactile

sense, pain), all of the dorsal horn lamina and ascending tracts of the spinal cord might potentially need to be considered, although those that mediate touch and proprioceptive information from the lower legs (e.g. fasiculus gracilis, anterior spinothalamic tract, nucleus dorsalis of Clark) are obviously more important. Within the brainstem and diencephalon, the nucleus gracilis in the medulla and the ventral posterior nuclear complex of the thalamus both mediate somatosensory information from the lower legs. In the cerebral cortex, the somatosensory cortex for the lower legs is on the part of the post-central gyrus that begins just dorsal to the cingulate gyrus, and ends on the cortical surface near the longitudinal fissure.

Opioid receptors are widely distributed within brain and spinal cord. In lumbosacral segments of the human spinal cord, there are dense concentrations of kappa receptors in Lamina II and III, while binding of ligands specific for mu and delta receptors is very low in all lamina (Gouarderes, Kopp, Cros, and Quirion, 1986). Quirion and Pilapil (1991) have reviewed the distribution of opioid receptors in the human brain in detail. According to their report, mu receptors are the most abundant opioid receptors, and are found in high

concentrations in the cerebellum, most basal ganglia structures, the amygdala, the motor and premotor cortices, the auditory cortex and inferior lobe in the temporal cortex, Brodmann's area 40 in the parietal lobe, and in the visual cortex. The distribution of delta receptors closely parallels that of mu receptors, except that they are not present in the cerebellum, and are present in high concentrations in the hippocampal formation. Kappa receptors are found in premotor, motor, and somatosensory cortices, some thalamic nuclei (specific nuclei were not mentioned), the amygdala, the hippocampal formation, the hypothalamus, the neostriatum, the pallidum, and the cerebellum. Thus, only the kappa receptor, and not the mu receptor, is localized in those areas mentioned above that mediate somatosensation in the lower legs, and these areas represent only a small portion of its total distribution within the brain. Thus, the anatomical distribution of paresthesias in RLS is difficult to explain in terms of the opioid theory. The intermittent nature of RLS and PLMS symptoms (e.g. their appearance at rest, their relief with movement, their circadian variation, and the periodicity of PLMs) are also difficult to understand in terms of the opioid theory, since the putative opioid deficiency (e.g. decreased receptor density) should

produce symptoms that are persistent rather than intermittent. The prevalence data are also difficult to understand in terms of the opioid theory, since none of the conditions in which a higher than normal prevalence of RLS or PLMS occurs has been associated with opioid abnormalities. Finally, the opioid theory can explain only a small part of the treatment data, since most of the drugs shown to be effective in RLS and PLMS are unlikely to affect opioid functioning within the CNS. In summary, although opioids are clearly effective in treating RLS, most of the well-established features of RLS and PLMS are difficult to understand in terms of this theory.

The putative dopamine abnormality in RLS and PLMS could consist of reduced dopamine levels, reduced number of receptors, impaired receptor functioning, or some combination of these factors. Much is known about the distribution of dopamine releasing neurons and dopamine receptors in the CNS (Bjorklund and Lindvall, 1984; Joyce and Murray, 1994), and some dysfunction of one or more of these pathways or receptors could be responsible for producing the paresthesias in RLS. There are eight major dopamine pathways in the mammalian CNS (Bjorklund and Lindvall, 1984), three of which potentially could be involved in RLS: the mesostriatal pathway, the

mesolimbocortical pathway, and the diencephalospinal pathway. The reduced D2 dopamine receptor density in the basal ganglia shown by Staedt et al. (1995) implicates the mesostriatal pathway in the pathogenesis of RLS. However, when dopamine release by this pathway is substantially decreased, symptoms of Parkinsonianism (e.g. rigidity, akinesia, bradykinesia) are the result (Adams and Victor, 1993). These symptoms are quite different from the paresthesias and motor hyperactivity seen in RLS. Blockade of dopamine receptors that are the targets of the mesolimbocortical dopamine neurons is believed to be the cause of neuroleptic-induced akathisia (NIA, Marsden and Jenner, 1980; Sachdev, 1995). As mentioned earlier, NIA does resemble RLS in some respects. Neuroleptic-induced akathisia is characterized by an inner sense of restlessness which leads to motor hyperactivity (Braude, Barnes, and Gore, 1983; Sachdev and Kruk, 1994). The motor hyperactivity is most commonly manifested in an inability to keep the legs still, body rocking, walking in place, and shifting position when seated. In addition, about half of all patients with akathisia do report abnormal leg sensations (Braude et al., 1983; Sachdev and Kruk, 1994). However, because the cortical projections of the mesolimbocortical pathway do not include the

somatosensory cortex (Bjorklund and Lindvall, 1984; Joyce and Murray, 1994), it is difficult to understand how a dysfunction of this pathway could produce the paresthesias seen in RLS. Several authors have suggested that the diencephalospinal dopamine pathway might be involved in RLS (Guilleminault et al., 1993; Sandyk, Iacono, and Bamford, 1988). This pathway has its cell bodies of origin in the hypothalamus, the zona incerta, and the caudal thalamus, and projects to the dorsal horn grey matter at all levels of the spinal cord (Bjorklund and Lindvall, 1984; Lindvall, Bjorklund, and Skagerberg, 1983). It is believed to be involved in pain modulation and in autonomic and motor responses (Lindvall et al., 1983). However, because it projects to all levels of the spinal cord, it is difficult to understand how a dysfunction in this pathway could produce a paresthesia that is restricted to the lower legs, excluding the feet. In summary, given the distribution of the three major dopamine pathways listed above, and the symptoms that are known to be caused by their dysfunction, it is difficult to understand how a dopaminergic dysfunction could cause the paresthesias seen in RLS. The intermittent nature of RLS and PLMS symptoms are also difficult to understand in terms of the dopamine theory for reasons similar to those

mentioned above for the peripheral neuropathy and opioid theories (i.e. a dopaminergic dysfunction should produce persistent rather than intermittent symptoms). As noted earlier, because iron deficiency causes reductions in dopamine receptor density (Ashkenazi et al., 1982), the dopamine theory can account for the higher than normal prevalence of RLS that is seen in conditions associated with iron deficiency (pregnancy, hemodialysis, gastrectomy). However, these conditions represent only a few of those in which a higher than normal prevalence of RLS and PLMS has been shown to occur. Similarly, the dopamine theory can only account for a small portion of treatment data as well, since many of the drugs effective for RLS and PLMS apparently do not affect dopamine pathways. In summary, although dopamine agonists are effective in treating RLS, and a small reduction in striatal dopamine receptor density has been demonstrated in RLS/PLMS patients, it is difficult to explain many of the features of RLS and PLMS in terms of the dopamine theory.

Before discussing the theory that RLS and PLMS are caused by oscillations of reticular system excitability, the anatomy and functions of this system should be reviewed briefly. The reticular system consists of the

reticular formation and its associated nuclei within the medulla, pons, and midbrain. Some of the more important nuclei are the gigantocellular nucleus, the oral and caudal pontine nuclei, the Raphe nuclei, and the locus coeruleus (Barr and Kiernan, 1993; Carpenter, 1991, pp. 212-215). This system begins caudally within the upper segments of the spinal cord, and ends rostrally in the midbrain. The reticular formation consists of numerous small groups of cell bodies that are extensively interconnected with each other and interspersed with white matter. Afferents to the reticular system originate in the cerebral cortex, the cerebellum, and the spinal cord (Carpenter, 1991, pp. 127-128). Sensory afferents include both spinoreticular fibers and axon collaterals that are given off by tracts transmitting information from cranial nerve nuclei as they ascend to the thalamus. Efferent projections include reticulospinal fibers, cerebellar projections, and projections to the cortex which are relayed via both thalamic and non-thalamic routes. The ascending cortical projections exert a potent arousing effect on the cortex, a finding which has led to the concept of the ascending reticular activating system. As reviewed by Carpenter (1991, p. 103), stimulation of the pontine and medullary reticular formation can exert a

variety of (descending) effects which include facilitation and inhibition of motor activity (including motor reflexes), changes in the level of muscle tone (mediated via the gamma system), changes in respiratory and cardiovascular activity, and facilitation and inhibition of the central transmission of sensory information from the spinal cord. The Raphe nuclei are also known to be involved in modulating pain sensation (Barr and Kiernan, 1993).

Given that the reticular formation can exert an influence on the transmission of sensory information from the spinal cord, it is plausible that this system might be involved in producing the paresthesia seen in RLS. However, the descending reticulospinal fibers originating in both the medulla and pons project to all levels of the spinal cord (Carpenter, 1991, pp. 101-103), so it is difficult to understand how oscillations in reticular system activity could cause a paresthesia that is restricted only to the lower legs. However, the intermittent nature of RLS and PLMS symptoms are potentially explainable in terms of the reticular system theory. For example, during inactivity and sleep, it is reasonable to assume that there is a reduction in afferent input to the reticular system (from both the sensory and

cortical afferents). Likewise, during waking activity (and perhaps during REM sleep), these inputs should be increased. In addition, as it will be noted in the next section, several periodic physiologic phenomena (blood pressure, respiration, and cortical arousal oscillations) have been shown to have a period similar to that of PLMs (20 to 40 seconds), and all of these phenomena could potentially be caused by oscillations in reticular system activity. Despite this, it is difficult to understand how the reticular system could directly cause PLMs, especially if it is correct that these movements are in fact Babinski responses (which are caused by damage to the corticospinal tracts rather than the reticulospinal tracts). The prevalence data are also potentially explainable in terms of the reticular system theory. Because most of these conditions have been associated with anemia or impaired oxygen transport secondary to impaired circulation, it is reasonable to assume that patients with many of these conditions may have altered levels of blood gases. Moreover, most brainstem neurons, including those of the reticular system are very sensitive to changes in blood gases (Dell, 1958; Jiang and Haddad, 1992). Thus, it is possible that many patients with secondary RLS might have alterations in blood gases, and consequently, reticular

system activity levels. The treatment data, however, are somewhat difficult to explain in terms of the reticular system theory. Many of the drugs effective in RLS (opioids, benzodiazepines, anti-convulsants) have well known depressant effects on the CNS, while dopamine agonists generally exert an arousing effect on the cerebral cortex and basal ganglia (Edvinsson et al., 1993, pp. 240-241). Given the opposing effects of these drugs on cortical (and reticular system) arousal levels, it is difficult to understand how they could all exert a therapeutic effect on RLS and PLMS via a reticular system mechanism. In summary, the reticular system theory can possibly explain some of the features of RLS and PLMS (especially the intermittent nature of the symptoms), but it is difficult to explain other features of the two disorders, particularly the anatomical distribution of paresthesias in RLS, in terms of this theory.

Smith (1985) proposed that PLMs were spontaneously occurring Babinski responses, and he suggested that they occurred during sleep because of a sleep-related reduction in descending pyramidal tract activity. Apart from these suggestions, Smith did little else in the way of attempting to integrate his theory with other theories of RLS and PLMS. He also did not attempt to explain how RLS

and PLMS might be related, and why some persons have these conditions while others do not. Moreover, because cortical activity, and descending inhibition from the pyramidal tracts, is at its lowest level during slow wave sleep, his theory is at odds with the data reviewed above which has shown that PLMs are most common in sleep stages 1 and 2. Despite this, Smith's observation that PLMs appear similar to the Babinski response was an important one, and it is generally well accepted.

In summary, none of the major theories of RLS and PLMS appears to be able to explain all of the well-established features of either disorder. The feature that appears to be the most difficult to explain is the localization of the paresthesias in RLS to the lower legs, excluding the feet.

Before turning to a detailed description of the periodic cerebral ischemia theory of RLS and PLMS, it will first be necessary to review the literature on a number of periodic physiologic phenomena that have been shown to have the same periodicity as PLMs. It will also be necessary to present a selected review of several general principles related to the control of cerebral blood flow. The next two sections are devoted to a review of these two topics.

Mayer Waves, B Waves, and Other Periodic Phenomena

Mayer Waves and Traube-Hering Waves

Mayer waves and Traube-Hering waves are both periodic oscillations of systemic blood pressure levels. In the case of Traube-Hering waves, the oscillations are synchronous with respiration, with one cycle of blood pressure oscillation occurring during each respiration. Traube-Hering waves are also known as second order blood pressure waves (first order waves are blood pressure oscillations associated with each heartbeat). Mayer waves are slower oscillations of blood pressure with a period of between 20 and 40 seconds in humans, and slightly less than this in cats and dogs. Mayer waves are also known as third order blood pressure waves. Both Mayer waves and Traube-Hering waves are vasomotor in origin; that is, they are caused by periodic vasoconstriction and vasodilation. Electrophysiologic studies have shown that the periodic vasomotor activity is synchronous with single unit activity in sympathetic vasoconstrictor fibers (Polosa, 1984; Preiss and Polosa, 1974), so it is generally accepted that the vasomotor oscillations have a neural rather than humoral or paracrine origin (for example, they are not caused by periodic release of endothelium-derived relaxing factor). Mayer waves have also been shown to be

accompanied by corresponding oscillations of blood flow volume, although the exact relationship is dependent on which vascular bed is studied (Killip, 1962). Killip found that during the systemic blood pressure peaks, blood flow in the aorta, muscles, and intestines was decreased, while blood flow in the skin and renal arteries was increased.

Traube-Hering waves are thought to be present continuously (Andersson, Kenney, and Neil, 1950; Koepchen, 1984), while Mayer waves are most commonly observed after an animal has had some sort of insult to the circulatory system (e.g. hemorrhage; Koepchen, 1984). Mayer waves are somewhat difficult to produce experimentally, although several methods (e.g. hemorrhage, complete or partial carotid artery occlusion, hypobaric ischemia, metabolic acidosis) can produce them reliably in experimental animals (Andersson et al., 1950; Ferretti et al., 1965; Miyakawa, 1984; Polosa, 1984b; Ueda et al., 1984). In addition, it has also been shown that Mayer waves can be elicited in spinal animals by increasing the CSF pressure in the subarachnoid space (Kaminski, Meyer, and Winter, 1970). In humans, Mayer waves have been recorded in patients with raised intracranial pressure and in normal subjects during sleep (Hayashi et al, 1984; Lugaresi et

al, 1972). Traube-Hering and Mayer waves are usually recorded from the femoral artery, but they have also been recorded in foot and pulmonary arteries (Ferretti et al, 1965; Hayashi et al., 1984), so it is likely that they occur throughout the peripheral vasculature. Oscillations of cerebral blood flow similar to and synchronous with peripheral Mayer waves have also been reported (Einhaupl et al., 1986; these are referred to as B-waves, and will be described in detail in the next section).

The amplitude of Traube-Hering waves is generally relatively small(e.g. about five to fifteen percent of the mean systemic pressure; Cherniak, Edelmann, and Fishman, 1969; Cherniak, Heymann, and Chisholm, 1967), while the amplitude of Mayer waves is much larger and more variable. For example, in hemorrhaged animals (with or without carotid artery occlusion) Mayer wave amplitudes of 25% to 80% of the mean arterial pressure have been reported (Andersson et al., 1950; Cherniak et al., 1969; Killip, 1962). In the human subjects studied by Lugaresi et al. (1972) the Mayer waves recorded during sleep had amplitudes ranging from 15 to 20 mm Hg (mean blood pressure values were not reported).

Several studies in experimental animals have found that the procedures used to produce Mayer waves also

produced periodic breathing that was synchronous with the blood pressure waves (Andersson et al., 1950; Killip, 1962; Preiss, Iscoe, and Polosa, 1975). This pattern of periodic breathing was characterized by a waxing and waning of tidal volume without actual apnea. Even though no periods of apnea were present, the waxing and waning of tidal volume was quite similar to that seen in Cheyne-Stokes breathing. The nadir of the tidal volume in these experiments was synchronous with the nadir of blood pressure; thus, the two oscillations were in phase with each other.

Both Traube (1865) and Hering (1869) proposed that blood pressure oscillations they observed were caused by an irradiation of excitation from medullary respiratory centers to medullary vasomotor centers. The finding that phenoxybenzamine administration abolishes Traube-Hering waves (Cherniak et al., 1969) is consistent with a vasomotor origin for the waves (as opposed to a fluid mechanics origin), and indirectly supports the original theories of Traube and Hering.

In his historical review of the literature, Koepchen (1984) pointed out that Mayer (1876) believed he had observed waves that were essentially the same as those reported by Traube and Hering despite the fact that they

were not synchronous with respiration. Other authors in the first half of this century disputed this, and showed that there were clearly two types of waves: one type that was synchronous with each respiration and since referred to as Traube-Hering waves, and one type with a longer period since referred to as Mayer waves (see Koepchen, 1984, for a review of this early literature). In the 1950s, 1960s, and 1970s, a number of studies were reported in which efforts were undertaken to determine the cause of the slower 20 to 40 second vasomotor oscillation. Based on those studies, two theories, the peripheral feedback and central oscillator theories, have emerged (Polosa, 1984).

Andersson et al., (1950) used hemorrhage combined with either unilateral or bilateral carotid artery occlusion to produce Mayer waves in cats. Because the waves could be abolished by either cooling or sectioning the vagus and carotid sinus nerves, Andersson et al. concluded that peripheral feedback from the chemoreceptors and baroreceptors was the source of the oscillations. In addition, because the mean systemic pressure in their animals was quite low (40 to 70 mm Hg), they concluded that afferent information from the chemoreceptors was more important than that from the baroreceptors. Guyton and

Harris (1951) performed experiments in which the baroreceptors were selectively denervated. This procedure either abolished or greatly reduced the amplitude of the Mayer waves, leading these authors to conclude that afferent feedback from the baroreceptors was more important than the feedback from the chemoreceptors. Armstrong and Irby (1962) used intra-arterial injections of acetic acid to destroy the carotid and aortic chemoreceptors, and found that Mayer waves persisted following this manipulation. When both the chemoreceptors and baroreceptors were destroyed, no Mayer waves could be elicited. Like Guyton and Harris (1951), Armstrong and Irby also concluded that the baroreceptors were more important than chemoreceptors in producing Mayer waves. In contrast to the findings by Armstrong and Irby (1962), two groups of researchers found that Mayer waves could persist after total denervation of the peripheral chemoreceptors and baroreceptors (Cherniak et al., 1969; Ferretti et al., 1965), although they were often reduced in amplitude. This suggested one of two possibilities; first, central chemoreceptors might be generating periodic excitation of the vasomotor centers; or second, a central oscillator might be providing periodic excitation to the vasomotor centers independent of the sensory input from

the chemoreceptors and baroreceptors. One of the experiments done by Ferretti et al. suggested that the first possibility was correct. In this experiment, injections of dilute hydrochloric acid were used to produce metabolic acidosis of sufficient intensity to cause Mayer waves in dogs that had undergone complete denervation of the chemoreceptors and baroreceptors. Subsequent injection of a buffer solution eliminated the Mayer waves. A later study by Preiss et al. (1975) found evidence which strongly suggested that a central oscillator was generating the Mayer waves. In this study, sympathetic nerve activity was found to be synchronous with the blood pressure oscillations. This sympathetic nerve activity persisted after several manipulations designed to eliminate rhythmic sensory input from both central and peripheral chemoreceptors and (peripheral) baroreceptors. These manipulations included simultaneous artificial ventilation to maintain constant blood gas levels, chemoreceptor and baroreceptor denervation, and alpha adrenergic blockage to eliminate the actual vasomotor oscillations. In other animals, the vasomotor oscillations were eliminated by connecting a pressure stabilizing device to the animals' aorta. The persistence of periodic sympathetic activity in spite of all these

manipulations indicated that although peripheral afferent mechanisms may have initially triggered the waves (the waves were produced by hemorrhage), they were not needed to maintain the periodic sympathetic output once the circulatory insult had occurred. The results of all of these experiments can be summarized by noting that there is evidence to support both the peripheral and central theories.

In spite of all this work, there is no clear consensus among researchers on how important the various central and peripheral mechanisms are in the generation of Mayer waves. Moreover, although there is some evidence to indicate that a central oscillator does exist, its precise anatomical location remains obscure. Langhorst, Schulz, and Lambertz (1984) and Lugaresi et al. (1972), among many others, have argued that the brainstem reticular formation represents this central oscillator. Unfortunately, there is little direct experimental evidence that reticular neurons have periodic oscillations in their firing rates with periods similar to those of Mayer waves. For example, Langhorst et al. (1984) recorded the spontaneous activity of medullary reticular neurons, and although some neurons with periodic firing were found, their period durations were usually about six seconds (this was twice

the respiration rate). It should be noted that Mayer waves were not observed in their animals, nor was there any attempt to generate them experimentally. Oakson and Steriade (1982) found oscillations in the firing rates of mesencephalic reticular neurons with periods varying between eight to twelve seconds (5 to 7.5 waves per minute). Of interest was the finding that these oscillations appeared only during quiet waking (i.e. wakefulness without movement) and non-REM sleep. Other investigators who have studied the firing rates of brainstem reticular neurons during the sleep-wake cycle have not found such oscillations (Manohar, Noda, and Adey, 1972; Vertes, 1979), although it is likely that methodological differences between these studies and that of Oakson and Steriade (1982) account for the negative findings (see Oakson and Steriade, 1982, for a review of the pertinent methodological issues). Despite this, it is worth emphasizing that oscillations of reticular neuron firing rates with periods longer than about 12 seconds have not been reported.

Another approach to studying firing rate rhythmicity was employed by Corner and Crain (1972). These investigators studied single unit activity of medullary neurons in slices of fetal tissue (from rodents) that were

maintained in vitro. The advantage of this technique was that the neurons studied were isolated from peripheral (i.e. chemoreceptor and baroreceptor) afferent input. About half of the neurons studied by these investigators showed periodicity in their firing. The majority of these neurons had active and inactive phases of approximately equal length, with the length of the total cycle varying between 1.0 and 5.0 minutes. Shorter period durations (always less than two minutes) were seen in two other periodically firing neurons in which the active phase was much shorter than the inactive phase. Unfortunately, the total number of neurons studied in this experiment was low (n = 39), and no detailed information on the anatomical location of the periodic neurons was provided. A more recent in vitro study of medullary neurons by Bingmann, Baker, and Ballantyne (1991) also found periodic neuronal activity, but the mean period duration of these neurons was 2.7 seconds (the range was 0.5 to 10 seconds). These authors noted that periodicity was not confined to any one anatomic region. They also suggested that the 2.7 second periodicity reflected the activity of respiratory-related neurons. In summary, these is very little direct experimental evidence to support the idea that neurons in

the reticular system have an intrinsic slow oscillation in their firing rates.

Still other work has shown that pharmacologic depression of the ventrolateral surface of the medulla (the central chemosensitive area) with lidocaine and benzodiazepines can abolish Mayer waves produced by hypoxia or hypercapnia (Haxhiu, Van Lunteren, Deal, and Cherniak, 1989). Other investigators have demonstrated that lesions of the area postrema in the dorsal medulla can also abolish Mayer waves (Pollick, Barnes, and Ferrario, 1987).

Finally, as mentioned earlier, a study by Kaminski et al. (1970) found that Mayer waves could be produced in spinal animals by increasing the subarachnoid CSF pressure. Kaminski et al. suggested that the increased pressure produced local spinal ischemia and a resulting excitation (and vasopressor response) of sympathetic neurons. They suggested that the resulting increased blood pressure improved spinal perfusion which then led to a decrease in sympathetic output and further oscillations of the system. The data from this study clearly indicate that spinal sympathetic vasomotor neurons are capable of periodic oscillations irrespective of their supraspinal afferent input. The issue of whether or not this

oscillation is due to a feedback mechanism or an endogenous periodicity in these neurons remains unresolved.

B Waves

The term "B wave" was introduced by Lundberg (1960) to refer to oscillations of intracranial pressure (ICP) with a frequency ranging from .5 to 2 per minute. In his 1960 study, Lundberg reported on his experience with continuous monitoring of ICP, and drainage of cerebrospinal fluid (CSF) to control this pressure, in a large sample of patients. These techniques were just coming into widespread clinical use at that time. In his report, Lundberg described three types of oscillations or short term increases in ICP. Lundberg initially referred to these as A, B, and C waves, and although he also proposed more descriptive names (plateau waves, one-per-minute waves, and six-per-minute waves, respectively), the term "B wave" has persisted in the literature. A-waves were large increases in ICP levels which usually lasted from five to twenty minutes. These were often accompanied by adverse neurological consequences. As mentioned earlier, B waves were ICP oscillations of variable amplitude which had a period ranging from about 30 seconds to about two minutes. In Lundberg's sample of patients

with intracranial hypertension, periods of approximately one minute predominated. C waves were relatively low amplitude ICP oscillations which occurred at a frequency of approximately six waves per minute. In contrast to A and B waves, C waves were observed only infrequently.

Two important observations with respect to B waves were pointed out by Lundberg (1960). First, the waves occurred most commonly during natural sleep and during periods of impaired consciousness, stupor, and coma. Second, like Mayer waves, B waves were frequently accompanied by Cheyne-Stokes respiration or periodic breathing, with the periods of apnea (or decreased tidal volume) occurring in phase with the low pressure points of the ICP tracing. Although the association of B waves and periodic breathing was common, B wave activity was also noted in some patients who were artificially ventilated. More recent studies have confirmed that B-waves may occur both with (Einhaupl et al., 1986; Hashimoto et al., 1989) and without (Einhaupl et al., 1986; Newell, Aaslid, Stooss, and Reulen, 1992) Cheyne-Stokes respiration or periodic breathing.

Lundberg (1960) proposed that both B and C waves were caused by oscillations of cerebral blood flow which led to corresponding oscillations of cerebral blood volume. He

suggested that B waves were caused by periodic vasodilation and vasoconstriction which occurred because of the oscillating blood gas levels produced by the Cheyne-Stokes respiration. However, Lundberg also noted that some authors (e.g. Hoff and Breckenridge, 1954) believed that Cheyne-Stokes respiration was due to an intrinsic brain stem rhythm, and he suggested that a similar rhythm affecting the vasomotor center might be responsible for generating the B waves that were observed in patients who were artificially ventilated. With respect to the C waves, Lundberg suggested that these were caused by oscillations of blood flow due to Traube-Hering waves (which he incorrectly referred to as Traube-Hering-Mayer waves). It should be pointed out that in the original studies by Traube (1865) and Hering (1869) the blood pressure waves that were observed had a frequency of about six per minute. It should also be noted that historically, the terms Traube-Hering waves and Mayer waves have often been used interchangeably; apparently because many researchers were not aware of the literature showing that these were two distinct phenomena (Koepchen, 1984). Although the predominant B wave frequency in Lundberg's patients was about one per minute, Lundberg did note that waves with frequencies in between those of B and

C waves (i.e. waves with frequencies between 2 and 4 per minute) sometimes occurred.

Although Lundberg's proposal that B and C waves were caused by oscillations in cerebral blood volume was generally well accepted, direct evidence to support this theory wasn't obtained until Auer and Sayama (1983) showed that B waves in experimental animals were accompanied by synchronous vasodilation and vasoconstriction of cerebral (pial) arteries.

Other more recent studies have shown that blood flow velocity in the middle cerebral artery (as assessed by transcranial Doppler sonography) shows oscillations that are synchronous with the B waves seen in the ICP tracing (Droste and Krauss, 1993; Mautner et al., 1989; Nakatani, Ozaki, Hara, and Mogami, 1989; Newell et al., 1992). These oscillations are in phase with each other, with increased flow velocity (and total blood flow volume) occurring during the periods of increased ICP. A number of researchers have used transcranial Doppler sonography (alone) to investigate whether or not similar oscillations of blood flow velocity occur in normal subjects. These studies have shown that B wave-like oscillations in blood flow velocity occur in the majority of subjects studied in both wakefulness (Mautner et al., 1989; Diehl, Diehl,

Sitzer, and Hennerici, 1991) and during sleep (Droste, Berger, Schuler, and Krauss, 1993). For example, Mautner et al. studied 20 normal subjects, and found that 16 had B wave activity. The mean amplitude of the B waves in these subjects was 9.2% of the mean blood flow velocity. In two subjects, amplitudes representing 19 and 21 percent of the mean flow velocity were found. Diehl et al. found mean B wave amplitudes of up to 30% of the mean flow velocity in the normal subjects they studied; and in addition, they reported that the amplitude of these B waves was significantly higher in a group of older subjects with a mean age of 70.0 years than a group of younger subjects with a mean age of 26.2 years (B waves were found in all subjects studied). Diehl et al. did not report group means for the period of the B waves in their normal subjects, but they did note that all subjects had B wave periods similar to one normal subject whose spectral analysis showed two B wave peaks representing periods of 37 and 150 seconds. Droste et al. (1993) found B wave periods during sleep which ranged from 20 to 75 seconds, and like Diehl et al., they also found that some subjects had two B wave peaks in their spectral analyses. For example, one subject whose data was presented graphically had B wave period peaks at 25 and 45 seconds.

Several studies have simultaneously monitored both ICP and systemic blood pressure in an attempt to determine if B waves occur synchronously with Mayer waves. Hayashi et al. (1984) found that B waves and Mayer waves (recorded from the femoral or foot arteries) occurred synchronously and in phase with each other (i.e. the peak of ICP occurred at the same time as the peak in systemic blood pressure) in most of their patients who had intracranial hypertension. Patients who were in terminal stages often had ICP B waves without any corresponding oscillations of systemic blood pressure. Newell et al. (1992) studied 20 patients with intracranial hypertension secondary to head injury, and found that B wave activity in the ICP and transcranial Doppler recordings was generally not accompanied by Mayer waves in the systemic blood pressure recordings. When both Mayer and B waves did occur, they were in phase with each other. Einhaupl et al. (1986) found that B waves and Mayer waves occurred in phase with each other 78% of the time in patients who had Cheyne-Stokes respiration and 72% of the time in patients who did not have Cheyne-Stokes respiration. Thus, B waves and Mayer waves were out of phase with each other about one fifth of the time in their patients. Hashimoto et al. (1989) found that B waves and Mayer waves occurred

synchronously and in phase with each other in 20 patients with raised ICP. They also noted that the B wave peak occurred shortly before the Mayer wave peak (by a few seconds). The recording site used for monitoring systemic blood pressure was not specified in their report.

In contrast to these studies in human patients, Higashi et al. (1989) found that B waves and Mayer waves did not occur in phase with each other in cats whose ICP was raised by infusion of mock CSF. The two waves were approximately 180 degrees out of phase (i.e. the B wave peaks corresponded to the Mayer wave troughs). This relationship was reversed only when the ICP was raised to the level of the systemic blood pressure. Simultaneous recording of unit activity from sympathetic nerves showed that distinct oscillations synchronous with the Mayer waves were present only during the experiments where the ICP was raised to match the systemic blood pressure. In these experiments the peaks of the sympathetic nerve discharge were synchronous with the troughs of the systemic blood pressure. This relationship was identical to that observed by Preiss and Polosa (1974) for Mayer waves produced by hemorrhage and carotid artery occlusion in cats. When Higashi et al. performed a bilateral cervical sympathectomy (i.e. the sympathetic innervation

to the cerebral vasculature was removed), the B waves persisted. This finding led Higashi et al. to suggest that an intrinsic noradrenergic pathway contained entirely within the brain mediated the B wave activity. These findings, taken together with those showing that B waves can occur in humans in the absence of Mayer waves, provide convincing evidence that neural pathways intrinsic to the brain may mediate the vasomotor oscillations that cause B waves. Reis (1984) reviewed evidence that several brainstem nuclei, including the dorsal medullary reticular formation and parabrachial nuclei in the pons, can exert potent influences on cerebral blood flow. Thus, it seems quite possible that separate neural pathways may mediate B waves and Mayer waves under at least some circumstances.

The research reviewed above has been conducted primarily by investigators whose main research interest was the study of intracranial hypertension in human patients. A separate line of work in experimental animals and humans was conducted in the late 1950s and the 1960s in which intracerebral electrodes were used to monitor oxygen availability and blood flow levels. Clark, Misrahy, and Fox (1958) conducted one of the earliest of these studies in experimental animals. Using chronically implanted platinum electrodes through which a small

electrical current was passed (i.e. polarographic electrodes), these researchers found oscillations of oxygen availability with a frequency of about six waves per minute and an amplitude of up to 30 percent of mean oxygen levels in unanesthetized cats. Waves recorded from several different sites in the same animal were usually not synchronous with each other. Moreover, the waves did not correspond to any observed oscillations in heart rate, respiration, or systemic blood pressure; thus, they were not Traube-Hering waves. Similar waves with a frequency of about six per minute were observed in human psychiatric and epileptic patients in a series of studies by a group of researchers in England (Cooper, Crow, Walter, and Winter, 1966; Moskalenko, Cooper, Crow, and Walter, 1964; Walter and Crow, 1964). The psychiatric patients studied by these workers were undergoing electrolytic frontal leucotomy, while the epileptic patients had the electrodes implanted for the purpose of identifying seizure foci. In addition to the six per minute waves in these patients, some of the figures presented by Cooper et al. (1966) appear to show slower waves with a period of about 50 seconds (for example, see Figure 2, p. 178, of Cooper et al., 1966). A later reanalysis of this data using spectral analysis showed that slower waves with a period

similar to that of B waves were indeed present in these subjects (Moskalenko, 1980, p. 122). Cooper and Hulme (1966) also implanted polarographic electrodes in a sample of 24 patients who were undergoing continuous monitoring of intracranial pressure. Like Lundberg, they observed both A and B waves, and noted that both were more common during sleep. The A waves occurred most commonly during REM sleep. The most important finding pertinent to this review is that the B waves were accompanied by synchronous oscillations of oxygen availability (see Cooper and Hulme, 1966, Figure 5, p. 567). In these instances, the peaks of ICP were associated with decreases in oxygen availability; thus, the two waves were approximately 180 degrees out of phase. In a later report, Cooper and Hulme (1968) showed that the ICP peaks which occurred during the B waves were also accompanied by bursts of slow wave activity in the EEG.

In summary, patients with intracranial hypertension frequently show oscillations of intracranial pressure which have a frequency ranging from .5 to 2 per minute. These so-called "B waves" are caused by oscillations of cerebral blood flow, and are more common during sleep than during wakefulness. Similar oscillations of cerebral blood flow (velocity) have been documented in normal human

subjects, and the amplitude of these waves has been shown to be larger in older subjects (Diehl et al., 1991). In patients with intracranial hypertension, these B waves are often accompanied by Mayer waves, Cheyne-Stokes respiration or periodic breathing, and periodic bursts of slow wave activity in the EEG. The synchronous occurrence of these phenomena suggests that they may all be caused by an intrinsic brainstem rhythm.

In November, 1996 a study was published by Droste, Krauss, Hagedorn, and Kaps (1996) in which B-waves of cerebral blood flow velocity were documented in four patients with PLMS. In this study it was found that the flow velocity values were significantly higher at the moment the PLMs occurred than during the interval between PLMs. Droste et al. concluded that B-waves and related oscillations in EEG activity (cyclic alternating pattern) were part of a common endogenous rhythm, and they further postulated that PLMs were an epiphenomenon of this rhythm. They did not elaborate on this, nor did they suggest that B-waves might cause PLMs, either directly or indirectly (e.g. by producing cerebral ischemia). This study is important because it provides the only direct evidence obtained thus far that abnormalities in cerebral blood flow (i.e. B-waves) are present in patients with PLMS.

The finding by Droste et al. (1996) that flow velocity was higher at the moment the PLMs occurred deserves additional comment. Previous work has shown that B-waves in flow velocity and intracranial pressure are in phase with one another (Droste and Krauss, 1993; Mautner et al., 1989; Newell et al., 1992). However, Cooper and Hulme (1966) found that B-waves in oxygen availability and intracranial pressure were 180 degrees out of phase (i.e. oxygen availability was low when intracranial pressure was high). Based on these studies, it is reasonable to assume that cerebral oxygen levels are lowest when blood flow velocity is highest. This also makes sense when one considers that low oxygen (and high CO_2) are potent vasodilators, and vasodilation lowers the resistance to blood flow, resulting in an increase in flow velocity. Thus, based on the data reported by Droste et al. (1996) it is reasonable to assume that PLMs occurred in their patients when cerebral oxygen levels were low. It should be noted though, that Cooper and Hulme (1966) studied psychiatric and epileptic patients; thus, it is unclear if their results are generalizable to normal subjects.

Cheyne-Stokes Respiration and Periodic Breathing

Cheyne-Stokes respiration (CSR) is a form of periodic breathing in which short periods of respiration alternate

with short periods of apnea (the total cycle duration varies from 0.5 to 1.5 minutes). When respirations are present, a characteristic waxing and waning of tidal volume is seen. Although the term periodic breathing has been used to refer to several forms of abnormal breathing (including central sleep apnea), it is most commonly used to refer to a pattern of respiration that is similar to CSR, but without periods of apnea (i.e. only a slow waxing and waning of tidal volume is observed). The original descriptions of these forms of abnormal respiration are attributed to Cheyne (1818) and Stokes (1854). A large number of studies investigating CSR have appeared since these early studies, and several excellent reviews of the CSR literature are available (Brown and Plum, 1961; Dowell, Buckley, Cohen, Whalen, and Sieker, 1971; Tobin and Snyder, 1984). The following review draws heavily from these sources.

Cheyne-Stokes respiration is seen clinically in several diseases. These include heart disease (including congestive heart failure), neurological disease (including intracranial hypertension and bilateral cortical damage), and uremia. Cheyne-Stokes respiration is also seen in premature infants and in normal human subjects undergoing acclimatization to high altitude. Cheyne-Stokes

respiration is often augmented during sleep, and periodic breathing of variable amplitude and duration is seen many normal subjects during sleep, especially near sleep onset (Robin, Whaley, Crump, and Travis, 1958; Bulow, 1963).

Most patients with CSR have both heart disease and neurological disease; however, CSR may occur if only one of these is present (Brown and Plum, 1961). Historically, the importance of heart disease versus neurological disease in the pathogenesis of CSR has been controversial. Stokes (1854) believed that CSR was always associated with heart disease. Heart disease is thought to cause CSR primarily by prolonging the lung to medullary chemoreceptor circulation times (Dowell et al., 1971). Brown and Plum (1961) described the clinical characteristics of CSR in detail in a sample of 28 patients. All 28 of their patients had neurological disease, while only 23 had heart disease. This finding led Brown and Plum to conclude that neurological disease was necessary for CSR to occur. Brown and Plum also found that their patients had average CO_2 levels that were lower than normal (i.e. respiratory alkalosis), and had ventilatory responses to CO_2 administration that were three times higher than those seen in normal subjects. They concluded that CSR was a pattern of "neurogenic

hyperpnea in which intense hyperventilation alternates with posthyperventilation apnea" (Brown and Plum, 1961; p. 859). They further suggested that the supramedullary neurological damage in their subjects was the source of the increased sensitivity to CO_2. This idea that neurological damage in CSR patients could produce an increased sensitivity of the medullary respiratory centers with subsequent hyperventilation had been suggested by several earlier workers, including Jackson (1895). This is in contrast to the opinion expressed by Hoff and Breckenridge (1954) that the neurologic damage in CSR released an intrinsic brainstem rhythm, which then resulted in a periodic activation of the medullary respiratory center.

A number of physiologic parameters alternate with respiration during CSR. With respect to blood gas levels, CO_2 levels are highest (and O_2 levels are lowest) during the hyperventilation phase (Dowell et al., 1971; Tobin and Snyder, 1984). The pupils usually dilate during the hyperpneic phase and constrict during the apneic phase; this reflects the predominant autonomic activity during each phase. In their 1971 review, Dowell et al. reported that the EEG is characterized by predominately fast activity during the hyperpneic phase and slow activity

during the apneic phase. Similarly, CSR patients are usually awake and responsive (and often agitated) during the hyperpneic phase, and confused, stuporous, and/or somnolent during the apneic phase (Dowell et al., 1971).

In patients with CSR, improvement in the underlying cardiac or neurological disease often eliminates the CSR, so the abnormal respiration itself is usually not treated. However, CSR can be eliminated with either respiratory stimulants, or by having the patient breath gas mixtures containing higher than normal amounts of either O_2 or CO_2 (Dowell et al., 1971; Tobin and Snyder, 1984).

In the 1950s and 1960s, several mathematical and computer models of CSR (and normal respiration) were developed in an effort to understand the causes of CSR. The first of these models, developed by Grodins, Gray, Schroeder, Norins, and Jones (1954), was an attempt to model the normal respiratory response to hypercapnia. This model used tissue CO_2 (rather than arterial CO_2) as the variable sensed by the respiratory controller. This model assumed that the sensor for CO_2 was the medullary respiratory center (i.e., peripheral chemoreceptors were neglected), and also assumed that circulation time was infinitely short (i.e., zero). The mathematical equations derived by Grodins et al. (1954) were used in simulations

of the ventilatory response to CO_2 administration, and the results obtained were in good agreement with available physiologic data from human subjects. This model was used a starting point by later investigators who attempted to model CSR.

Millhorn and Guyton (1965) were to first to develop a computer model of the respiratory system in which CSR could be produced. In their model CSR could only be produced if either the arterial circulation time or the controller gain was manipulated. The "controller gain" refers to the amplitude of the ventilatory response (to CO_2 for example). Increases in this variable could be mediated physiologically by either respiratory motor neurons or sensory neurons which monitor blood gas levels. Millhorn and Guyton found that their model could produce sustained CSR if the circulation time was increased to three and half minutes or if the controller gain was increased to 13 times its normal value. Both of these values were obviously larger than those that were likely to be occurring in CSR patients, a problem which suggested inadequacies in their model.

Longobardo, Cherniack, and Fishman (1966) presented a model similar to that of Millhorn and Guyton (1965), and found that CSR could be induced in this model under

conditions similar to those in which it occurred physiologically (e.g. sustained hyperventilation in normals, congestive heart failure, neurologic disorders, and altitude acclimatization). However, in the simulation of hyperventilation in normals, the model had to be hyperventilated to a very low arterial CO_2 value of 14 mm Hg before CSR occurred, and in the simulated congestive heart failure condition (simulated by increasing the circulation time and decreasing the cardiac output), the model also had to be hyperventilated before CSR occurred. Overall, the results were similar to those obtained by Millhorn and Guyton in that the model showed that there were only two types of CSR, one caused by abnormal circulation times, and one caused by abnormal CO_2 sensitivity. It should be pointed out that neither of these two models (Millhorn and Guyton, 1965; Longobardo et al., 1966) included peripheral chemoreceptors.

Khoo, Kronauer, Strohl, and Slutsky (1982) presented a model which included peripheral chemoreceptors, and which was also based on different mathematics than the earlier models presented above. The peripheral (carotid) chemoreceptors in this model were designed to respond to arterial O_2 levels. CSR could be produced in this model by a combination of relatively mild hypoxia and

hypercapnia, similar to that seen in many subjects during sleep. The model also produced CSR when cardiac and neurological disease were simulated with abnormally long circulation times and abnormal controller gains respectively. Overall, the results indicated that the peripheral chemoreceptor input was relatively important in mediating CSR. In addition, the deviations in model parameters needed to produce CSR were much closer to those known to be present in actual CSR patients.

It should be pointed out that in none of the three models presented above was it necessary to include external oscillatory input (i.e. a brainstem oscillator) to produce CSR. CSR was produced in these models by directly manipulating the parameters of the respiratory system alone (sensors, output units, etc). Thus, the data obtained from these models is inconsistent with the idea of Hoff and Breckenridege (1954) that CSR is caused by disinhibition or release of an intrinsic brainstem rhythm.

Cyclic Alternating Pattern

Cyclic alternating pattern (CAP) is a term coined by Terzano, Mancia, Calzetti, Zachetti, and Maione (1981) to refer to oscillations in EEG activity occurring in coma and natural sleep. These oscillations have a period which averages about 40 seconds in normal subjects (Terzano and

Parrino, 1993). According to the scoring system developed by Terzano, CAP cycles are divided into two phases; Phase A reflects arousal and comprises approximately one third of the total cycle, and Phase B reflects decreased arousability and comprises approximately two thirds of the total cycle time (Terzano et al., 1985; Terzano and Parrino, 1993). The variation that is observed in the EEG activity during CAP sequences depends on the sleep stage (Terzano et al., 1985). In Stage 1, Phase A consists of alpha activity, while Phase B consists of the normal mixed frequency theta background. In Stage 2, Phase A consists of K complexes with associated alpha activity and alpha arousals, while Phase B consists of the normal Stage 2 background activity with isolated K-complexes. In Stages 3 and 4, Phase A consists of sequences of K-complexes and/or reactive delta waves, while Phase B consists of the normal amount of (randomly distributed) delta activity. CAP was not identifiable in REM sleep (Terzano et al., 1985). In comatose patients, Phase A is characterized by high amplitude slow wave activity which appears similar to the delta activity occurring during slow wave sleep. Phase B is characterized by relatively fast medium voltage activity (Evans, 1976; Terzano et al., 1981).

Although Terzano and his colleagues have done the most extensive work on CAP, a number of earlier investigators had described this phenomenon in both animals and humans. Bonvallet, Dell, and Hiebel (1954) recorded both EEG and blood pressure in anesthetized cats and dogs. They observed a simultanecus oscillation of both the EEG and blood pressure when the animals were not being subjected to any sensory stimulation. The activation in the EEG was synchronous (i.e. in phase) with the increases in blood pressure. A series of brainstem sectioning experiments indicated that the EEG arousal was being produced by the ascending reticular activating system (ARAS) in the rostral portions of the reticular formation, although Bonvallet et al. did not rule out the possibility of a humoral origin for the EEG waves. Similar oscillations of EEG activity during six per minute waves in rats have been described more recently by Golanov, Yamamoto, and Reis (1994).

Poole (1960) briefly described oscillations of EEG activity in two patients with subacute encephalitis. The EEG waves were synchronous with oscillations of respiratory activity, but it was not stated if the respiratory oscillations were Cheyne-Stokes respiration. A more detailed description of EEG oscillations in

comatose patients was provided by Evans (1976). The oscillations in these patients had a period which varied from 0.5 to 2.0 minutes, and they were synchronous with oscillations in heart rate and respiration rate. Evans noted the similarity of the EEG oscillations he described and the B waves described by Lundberg (1960). His paper is noteworthy in that it is the only paper in which the similarities of Mayer waves, B waves, Cheyne-Stokes respiration, and oscillations in EEG activity were specifically discussed. Despite this, Evans was hesitant to speculate on a pathogenic mechanism by which these phenomena might be interrelated, although he did note that previous investigators (including Lugaresi) had suggested that an intrinsic brainstem rhythm might be the source of these phenomena.

Terzano and his colleagues first described CAP in patients with Creutzfeldt-Jakob disease (Terzano et al, 1981), but they subsequently found that CAP occurred in both normal subjects (Terzano et al., 1985), and in patients with epilepsy (Terzano, Parrino, Anelli, and Halasz, 1989), insomnia (Terzano and Parrino, 1992), sleep apnea (Terzano, Parrino, and Spaggiari, 1990), and most recently in PLMS (Terzano and Parrino, 1993; Terzano, Parrino, Boselli, Di Giovanni, and Spaggiari, 1995).

Montplaisir, Lapierre, and LaVigne (1994) also described periodic oscillations in EEG activity in RLS/PLMS patients. In this study, the oscillations were observed during both sleep and wakefulness (during a Forced Immobilization test). Both Terzano et al. (1995) and Montplaisir et al. (1994) noted that leg movements during sleep occurred in association with arousal, a finding which led Terzano et al. (1995) to propose that the arousal phase of CAP promoted the appearance of PLMs. However, Montplaisir et al. (1994) found that leg movements during wakefulness were associated with EEG slowing. This finding led Montplaisir et al. to conclude that leg movements in RLS and PLMS required a critical level of cortical arousal to appear. They further suggested that this critical level of arousal appeared during drowsiness in wakefulness (as indicated by EEG slowing), and during arousal in sleep. Also of interest was a recent study by Montplaisir, Boucher, Gosselin, Poirier, and LaVigne (1996) which found that periodic K-alpha arousals in RLS patients persisted after L-DOPA treatment even though nocturnal leg movements had been eliminated. Montplaisir et al. suggested that these data indicated that the periodic EEG arousal (CAP) was a primary phenomenon in RLS patients.

The data obtained by Terzano and colleagues on CAP in normal subjects is noteworthy in several respects. First, CAP sequences occupy a significantly greater percentage of both total sleep time and non-REM sleep time in older subjects (38 to 50% of NREM time) than in younger subjects (18 to 25% of NREM time; Terzano et al., 1987; Terzano and Parrino, 1993). As noted earlier, the average cycle duration is 40 seconds (the standard deviation is approximately 23 seconds); however, the duration is longer in Stage 1 (54 seconds) than in Stages 2, 3, and 4 (range 38 to 39 seconds). CAP sequences were not identifiable in REM sleep. Approximately two thirds of CAP sequences occur during the first half of the night. The percentage of CAP time during each sleep stage was as follows: Stage 1 - 57%, Stage 2 - 21%, Stage 3 - 31%, Stage 4 - 16% (Terzano et al., 1985). Some aspects of this CAP data are similar to PLMS data (e.g. CAP being more frequent in older subjects and apparently not present in REM sleep), while others are not (e.g. the cycle duration and sleep stage percentages).

One serious problem with the definition and scoring of CAP as developed by Terzano and his colleagues is that arousals caused by apneas and PLMs and the subsequent return of normal sleep EEG activity would be (and are)

scored as CAP cycles. Thus, based on the scoring system developed by Terzano et al. (1985), no distinction is made between spontaneous periodic arousals, and those caused by specific events occurring during sleep. Both types of arousals would be scored as Phase A of CAP sequences. As mentioned above, Montplaisir et al. (1996) found that periodic arousals persisted in RLS patients even after leg movements had been eliminated with L-DOPA treatment. Although this did suggest that the arousals might be a primary phenomena, Montplaisir et al. also noted that PLMs recorded during a baseline night were associated with arousals only 49% of the time. Moreover, when the movements were associated with arousals, the arousals followed the leg movements 65% of the time (indicating that the movements generally caused the arousals). In summary, the scoring of arousals associated with apneas and PLMs as part of CAP sequences seems somewhat questionable. None-the-less, CAP is one of only two periodic phenomena discussed in this review which has actually been documented to be associated with RLS and PLMS (Montplaisir et al., 1994; Terzano et al., 1995).

Summary and Integration

The four phenomena discussed above, Mayer waves, B waves, periodic respiration, and cyclic alternating

pattern are related in several important ways. First, as noted above, two or more of these phenomena often occur simultaneously, both in human patients and in experimental animals. Second, as it will be discussed in more detail below, all of these phenomena are mediated by the brainstem reticular formation. Third, with the possible exception of Mayer waves, all of these phenomena are more likely to appear during sleep (or in patients with supramedullary neurological damage) than wakefulness.

The neural centers that mediate vasomotor functions, respiration, and cortical arousal are all located within the brainstem and are either coextensive with or receive input from several nuclei of the reticular formation. The brainstem vasomotor centers include a pressor region which begins rostrally in the pons (just below the cerebellar peduncles) and ends caudally in the medulla at about the level of cuneate nucleus (Gebber, 1980). At the level of the pons, the pressor region extends across the entire brainstem, but at the pontine/medullary junction the depressor region begins (it extends to caudal levels of the medulla), and occupies medial areas of the brainstem, while the pressor region flanks its lateral borders (see Gebber, 1980, Figure 1, p. H144). In the dorsoventral plane, both regions occupy almost the entire dorsoventral

extent of the brainstem at rostral levels, then become limited to the medial portions of the brainstem at the level of the medulla. These regions occupy fairly large areas within the brainstem, and are coextensive with the caudal pontine nucleus, the gigantocellular reticular nucleus, the parvocellular reticular area (which is just lateral to the gigantocellular reticular nucleus in the medulla), and the lateral reticular nucleus.

The respiratory centers are much more limited in their extent, and consist of two dorsomedially located dorsal respiratory groups which contain primarily inspiratory neurons, and two ventrolaterally located ventral respiratory groups which contain primarily expiratory motor neurons (Ganong, 1995; pp. 615-616). Both groups begin rostrally near the level of the obex, but the ventral respiratory groups extend caudally about twice the length of the dorsal respiratory groups to the caudal extent of the medulla. The dorsal respiratory groups are located in and near the caudal portions of the nucleus of the solitary tract, while the ventral respiratory groups are located in and near the nucleus ambiguus and the nucleus retroambiguus. Although these groups are not coextensive with nuclei of the reticular formation, stimulation of various reticular nuclei can

exert an influence on them. Stimulation of the gigantocellular reticular nucleus in the medulla augments inspiration, while stimulation of the more laterally located parvocellular reticular area augments expiration (Barr and Kiernan, 1993). Orem (1994) has suggested that the reticular formation comprises part of the anatomical substrate for the so-called wakefulness stimulus on respiration. The decreased ventilatory response to CO_2 that is observed during sleep (Birchfield and Sieker, 1959) is one manifestation of this respiratory wakefulness stimulus system. In addition to these medullary centers, there are also a pair of pneumotaxic centers located in the pons; these are coextensive with the medial parabrachial nucleus and the Kollicker-Fuse nucleus, and appear to mediate the duration of both the inspiratory and expiratory phases of respiration (Ganong, 1995, pp. 616-617; Orem, 1994). Finally, there are several areas on the ventral surface of the medulla that are chemosensitive zones, the most well documented of these being the ventrolateral medullary surface (Millhorn and Eldridge, 1986). Neurons in this area project to (and influence) both respiratory centers and vasomotor centers (Millhorn and Eldridge, 1986).

The concept of the ascending reticular activating system (ARAS) was first proposed by Moruzzi and Magoun (1949), and was based on studies in which it was shown that electrical stimulation of the brainstem reticular formation exerted a potent arousing influence on cortical activity. This initial work showed that stimulation of the reticular formation along almost all of its entire rostrocaudal extent (i.e. mesencephalon to medulla) could elicit EEG activation. Later studies have shown that the mesencephalic reticular neurons are most responsible for this arousing effect (Steriade, 1996; Steriade, Oakson, and Ropert, 1982; Steriade, Ropert, Kitsikis, and Oakson, 1980).

Thus, vasomotor activity, respiration, and cortical arousal are all mediated by or influenced by the activity of the brainstem reticular formation. Because neurons in the reticular formation are extensively interconnected (Barr and Kiernan, 1993), it is perhaps not surprising that two or more of the periodic phenomena discussed above often occur simultaneously. The issue of how this happens (and why it is more likely to happen during sleep or coma) is less clear, but there are at least two possible explanations.

The first of these is the idea that neurons in the brainstem reticular formation have an intrinsic slow rhythm that becomes relatively more prominent when afferent input to the reticular formation is reduced. Because the reticular formation receives substantial afferent input from both the cerebral cortex and from sensory systems (Barr and Kiernan, 1993; Carpenter, 1991, pp. 127-128), it is reasonable to assume that a substantial reduction of this input occurs during sleep and coma. The postulated inherent slow rhythm would then become more prominent, and would be reflected by oscillations in the physiologic parameters that are mediated by the reticular formation (e.g., arousal, respiration, cardiovascular activity). Unfortunately, as noted earlier, there is very little direct experimental evidence to support the idea of an intrinsic slow rhythm in the firing rate of reticular neurons, although the studies mentioned earlier (Manohar et al., 1972; Oakson and Steriade, 1982; Steriade et al., 1982, Vertes, 1979) did find that most reticular neurons have a substantial decrease in their firing rate in non-REM sleep as compared to wakefulness and REM sleep.

The second explanation is that wakefulness exerts a tonic excitatory influence on the vegetative functions of

respiration, cardiac activity, vasomotor functions, and arousal level. This wakefulness stimulus is transmitted from the cortex and peripheral sensory systems to the brainstem areas mediating the physiologic functions mentioned above by the reticular formation. Removal of this wakefulness stimulus could then be expected to alter the properties of one or more of the components of the systems regulating these functions, making the system more unstable and more likely to oscillate. Each system could be affected independently, or they could all be affected simultaneously, depending on the nature and extent of the removal of the wakefulness stimulus (i.e. whether it was due to natural sleep or to neurological damage).

With respect to respiration, the wakefulness stimulus is thought to be mediated by both the reticular formation and by various forebrain structures, including the limbic system and motor areas in the frontal lobe (Orem, 1994). The removal of this stimulus is reflected physiologically by a decrease in ventilation during sleep (by about 15% in slow wave sleep; Krieger, 1994), a reduced ventilatory response to CO_2 during sleep (Birchfield and Sieker, 1959), and by the observation that it is easier to produce post-hyperventilation apnea during sleep or anesthesia than it is during wakefulness (Krieger, 1994). In

contrast to these data (which indicate a reduction in respiratory drive during sleep) are the findings of Brown and Plum (1961) in patients with coexisting neurological damage and Cheyne-Stokes respiration. These investigators found that neurological damage caused an increased ventilatory response to CO_2, and suggested that supramedullary centers exerted a tonic inhibitory influence on respiratory sensitivity. None-the-less, the idea that the sensitivity of the respiratory system varies during the sleep-wake cycle in neurologically intact subjects is a well established principle (Krieger, 1994; Orem, 1994). Moreover, as mentioned above, when sleep related changes in chemosensitivity and blood gas levels are simulated in computer models of the respiratory system, periodic breathing can be produced (Khoo et al., 1982).

This idea of the wakefulness stimulus can be extended to the regulation of cardiac and vasomotor functions (and to a somewhat lesser extent, arousal). Unfortunately, there is no available information on changes in vasomotor functions and reflexes (such as the baroreceptor reflex or the cardiovascular response to passive tilting) during the sleep-wake cycle. Although there are reductions in both heart rate and blood pressure during non-REM sleep

(Littler et al., 1975; Millar-Craig et al., 1978), like the changes in ventilation, these may be secondary to reductions in metabolic rate during non-REM sleep, rather a reflection of an altered sensitivity of the cardiovascular system or one of its components. Despite this, the regulation of vasomotor tone is similar to the regulation of respiration in that both are based on negative feedback systems; thus, removal of the wakefulness stimulus might be a plausible explanation for the sleep-related appearance of B-waves and Mayer waves in addition to that of periodic breathing.

As mentioned earlier, it is common for one or more of the periodic phenomena discussed above to occur together. However, only the cyclic alternating pattern and B-waves have been shown to be present in patients with RLS and/or PLMS (Droste et al., 1996; Montplaisir et a., 1994; Terzano et al., 1995), and it is unclear from these studies how these phenomena might actually cause RLS and/or PLMS, or if in fact they even do. The periodic cerebral ischemia theory of RLS proposes that B-waves are present in both RLS and PLMS, and that they represent the one of the primary physiologic mechanisms responsible for producing both disorders. Because B-waves and Mayer waves are closely related (i.e. both are vasomotor waves), it is

possible that Mayer waves might also be present in RLS and PLMS. Despite this possibility, neither Mayer waves nor periodic breathing have been shown to be present in RLS/PLMS. Thus, the question of why B-waves and CAP would be present in RLS/PLMS while Mayer waves and/or periodic breathing would not be present has to be asked. Unfortunately, there is no easy answer to this question. One possibility is that removal of the wakefulness stimulus affects vasomotor functions to a greater extent than respiratory functions because the vasomotor centers of the brainstem are more extensive than those of the respiratory centers. Another possibility is the brainstem centers that generate vasomotor waves and CAP are more intimately associated with the reticular formation than are the centers that generate the respiratory rhythm.

Regulation of Cerebral Blood Flow: A Selected Review

Some Basic Principles

In this section, the anatomy and innervation of the cerebral vasculature will be briefly reviewed, and two basic principles which govern the regulation of cerebral blood flow, autoregulation and flow-metabolism coupling, will be briefly discussed.

Blood flows into the cranial vault via two pairs of arteries: the internal carotid arteries which are located anteriorly, and the vertebral arteries which are located posteriorly. At the level of the caudal pons the paired vertebral arteries join to form the basilar artery. Before bifurcating near the mammillary bodies to form the posterior cerebral arteries, the basilar artery gives off three large pairs of arteries: the anterior inferior cerebellar arteries, the labyrinthine arteries, and the superior cerebellar arteries. The anterior inferior cerebellar arteries and the superior cerebellar arteries supply the cerebellum, while the labyrinthine arteries supply the cochlea and vestibular apparatus (Carpenter, 1991, pp. 449-455). Each of the posterior cerebral arteries divides into two main branches, the posterior temporal artery which supplies part of the ventral surface of the temporal lobe, and the internal occipital artery

which supplies most of the occipital lobe and part of the parietal lobe.

Just lateral to the optic chiasm, the internal carotid arteries bifurcate to form the middle and anterior cerebral arteries. The middle cerebral arteries are the largest of the cerebral arteries, and represent a continuation of the internal carotid arteries. Each middle cerebral artery passes between the medial aspect of the temporal lobe and the insula, and gives off a large number of branches which emerge from the lateral sulcus. These branches spread out over the surface of the cerebral cortex, and supply large areas of the frontal, temporal, and parietal lobes.

The anterior cerebral arteries course medially from their point of origin, and then enter the longitudinal cerebral fissure at the midline. The anterior arteries are also connected to one another at the midline via the small anterior communicating artery. Each anterior cerebral artery gives off three large branches and two small branches. The large branches include the frontopolar artery which supplies medial areas of the frontal lobe, the callosomarginal artery which supplies the paracentral lobule and dorsal parts of the cingulate gyrus, and the pericallosal artery which supplies medial

areas of the parietal lobe. The small branches of the anterior cerebral artery include the medial striate artery which supplies the anterior parts of the caudate nucleus and internal capsule, and the orbital artery which supplies orbital and medial surfaces of the frontal lobe.

The posterior cerebral arteries are connected to the internal carotid arteries via the posterior communicating arteries near the point where the carotids bifurcate into the middle and anterior cerebral arteries. This connection between the posterior cerebral arteries and the internal carotids along with the connection between the two anterior cerebral arteries forms the Circle of Willis. There is normally little or no blood flow through the posterior communicating arteries because the pressure in the posterior cerebral arteries and the internal carotids is nearly equal (Carpenter, 1991, p. 440).

At the boundaries of the territories perfused by the three major cerebral arteries in each hemisphere there are arterial anastomoses through which the terminal branches of the three major cerebral arteries are interconnected (Edvinsson, MacKenzie, and McCulloch, 1993, p. 13; Vander Eecken and Adams, 1953). These anastomoses are believed to provide a collateral source of blood flow to ischemic regions in the event of an occlusion in one of the major

arteries (Vander Eecken and Adams, 1953). It has also been suggested that the presence of these anastomoses makes the boundaries of the territories perfused by the major cerebral arteries dynamic rather than static (Van der Zwan, Hillen, Tulleken, Dujovny, and Dragovic, 1992). For example, Van der Zwan and Hillen (1990) found that the boundary of the anterior cerebral artery could be shifted laterally over the cortical surface by a distance of three centimeters if the perfusion pressure in the middle cerebral artery was suddenly reduced. Van der Zwan et al. (1992) also found that there was a large degree of individual variability in the territories perfused by the major cerebral arteries.

The venous drainage of the brain is accomplished primarily via a series of large venous sinuses which are actually spaces between the periosteal and meningeal layers of the dura mater. These dural sinuses receive and drain a large number of smaller veins which run along the surface of the cerebral cortex. The principle venous sinuses include the superior sagittal sinus which runs along the longitudinal cerebral fissure in the falx cerebri, and the paired transverse sinuses which run between the cerebellum and occipital lobe in the tentorium cerebelli. Other dural venous sinuses include the

inferior sagittal sinus, and the occipital sinus. The transverse sinuses run laterally and rostrally around the cerebellum, and then turn medially to become the sigmoid sinuses. The sigmoid sinuses empty into the large paired internal jugular veins. The internal jugular veins also drain the cavernous sinus, a network of veins which surrounds the pituitary gland and other diencephalic structures. The cavernous sinus receives blood from several large veins and sinuses including the middle cerebral veins, the sphenoparietal sinuses, and the superior and inferior petrosal sinuses (Carpenter, 1991, p. 457).

The innervation of the cerebral vasculature has been reviewed in detail by Edvinsson, MacKenzie, and McCulloch (1993, pp. 57-91) and can be briefly summarized as follows. Sympathetic (vasoconstrictor) fibers arise from the superior cervical and stellate ganglia, and release the neurotransmitters norepinephrine and neuropeptide Y. Parasympathetic (vasodilator) fibers arise from the sphenopalatine and otic ganglia, and release acetylcholine and vasoactive intestinal polypeptide. There is also a serotonergic innervation that arises from the raphe nuclei; these fibers exert a vasodilatory influence when vascular tone is high and a vasoconstrictor influence when

vascular tone is low. Finally, there are sensory nerve endings on the cerebral vessels which have their cell bodies in the trigeminal ganglia. These fibers release substance P, neurokinin A, and calcitonin gene-related peptide from their axon terminals which synapse on second order neurons in the brainstem.

It should also be pointed out that dopamine D1 and D2 receptors have been localized within all layers of cerebral arteries, and stimulation of these receptors causes vasodilation (Amenta, Ricci, and Vega, 1991; Bacic, Uematsu, McCarron, and Spatz, 1991). The source of the dopamine that binds to these receptors is unclear (e.g. axonal endings, CSF), although there is some evidence of a dopaminergic innervation of the cerebral vasculature (Edvinsson, MacKenzie, and McCulloch, 1993, pp. 231-233). In addition, dopamine receptors have also been localized in peripheral vessels, particularly those in the kidney, and are believed to play a role in the regulation of fluid volume (Lokhandwala and Chen, 1994).

The brain is one of several organs in which blood flow is autoregulated. This term refers to the ability of an organ to regulate its own blood flow (Ganong, 1995; p. 542). In the case of the brain, it specifically refers to the observation that fairly constant levels of total blood

flow are maintained over a range of systemic blood pressure values which vary from 60 to 140 mm Hg (Edvinsson, MacKenzie, and McCulloch, 1993, p. 553; Ganong, 1995, p. 563). Above and below those blood pressure values, total cerebral blood flow varies directly with the perfusion pressure. There are three theories concerning the mechanism of autoregulation: the myogenic theory, the metabolic theory, and the neurogenic theory (Edvinsson et al., 1993, pp. 565-570).

The myogenic theory proposes that autoregulation is an intrinsic property of vascular smooth muscle. According to this theory, as pressure on the arterial wall increases, there is a corresponding contraction of the vascular smooth muscle (and vice-versa with respect to decreased pressure). As noted by Edvinsson et al. (1993, pp. 565-567), the intracellular and biochemical mechanisms by which this is accomplished remain unclear. Despite this, the myogenic theory of autoregulation is generally well accepted.

The metabolic theory of autoregulation proposes that global (or regional) reductions in blood flow result in an increased production of vasodilator metabolites which act to restore blood flow to adequate levels. This theory is thus a flow-metabolism coupling theory, although it should

be noted that the term flow-metabolism coupling is generally used to refer to regional variations in cerebral blood flow that occur in response to regional changes in metabolic rate. Although this theory can potentially explain the dilatory response to reduced blood flow, it does not address the contractile response to increased blood flow (and/or increased systemic blood pressure), and is thus an incomplete explanation for the phenomenon of cerebral autoregulation.

The neurogenic theory of autoregulation proposes that the innervation of the cerebral vasculature (including the sensory nerve fibers and possibly peripheral baroreceptors as well) mediates autoregulation. According to this theory, perfusion pressure is sensed by either peripheral baroreceptors or cerebrovascular sensory nerves, and corresponding adjustments in vascular tone are effected by the autonomic innervation. However, when either afferent or efferent fibers in these putative circuits are sectioned, the capacity for autoregulation remains (McCulloch, 1988), so this theory has poor empirical support. In summary, cerebral blood flow is maintained at fairly constant levels accross a wide range of perfusion pressures. This autoregulation of cerebral blood flow is

thought to be effected primarily by intrinsic contractile properties of cerebrovascular smooth muscle.

Another well-established principle of cerebral blood flow is that regional blood flow is closely coupled to regional metabolic rate. The same principle also applies to global cerebral blood flow and metabolism. The existence of flow-metabolism coupling has been established by a number of indirect lines of evidence (e.g. cerebral blood flow is low during coma and high during seizures; see Reivich, 1974, for a review), and by more rigorous studies in which it has been demonstrated that there are high correlations between regional glucose or oxygen uptake and regional blood flow when both variables are measured simultaneously (Buxton and Frank, 1997; Ginsberg, Smith, Wachtel, Gonzalez-Carvajal, and Busto, 1986). Most of the early work in which both cerebral metabolic rate and cerebral blood flow were measured simultaneously was done with either anesthetized animals or under resting conditions with human subjects. More recent studies using positron emission tomography and functional MRI have found that cerebral blood flow apparently increases to a much greater extent than cerebral metabolism (i.e. oxygen uptake) during functional activation produced by somatosensory stimulation and mental tasks (Buxton and

Frank, 1997; Fox and Raichle, 1986; Hedera et al., 1995). These studies were initially interpreted as representing an uncoupling of flow and metabolism during functional activation (Fox and Raichle, 1986). However, Buxton and Frank (1997) recently presented a mathematical model of cerebral oxygen delivery in which small increases in metabolic rate were accompanied by relatively large increases in blood flow. This model indicated that the disproportionately large increases in cerebral blood flow seen during functional activation are in fact reflective of a tight coupling (rather than an uncoupling) of cerebral blood flow and metabolism. Critical to the model was the assumption that increases in cerebral blood flow are effected primarily by increases in blood flow velocity rather than by recruitment of previously closed capillaries (see Buxton and Frank for evidence in support of this assumption). The increased flow velocity lowers the amount of oxygen that can be extracted from the blood because the transit time of the blood through the capillaries is decreased. This model is important because it can explain the confusing earlier evidence of flow-metabolism uncoupling during functional activation.

It is generally well-accepted that flow-metabolism coupling is mediated by an increased regional (or global)

production of metabolic by-products which have a vasodilatory effect (Edvinsson et al., 1993, pp. 567-568; Ganong, 1995, pp. 560-563). These so-called vasodilator metabolites include hydrogen ions (lowered pH), decreased O_2, increased CO_2, potassium ions, and adenosine, although it is unclear which of these is most important (Edvinsson et al., 1993, pp. 567-568). Hypoxia and hypercapnia that result from systemic disease, such as COPD or anemia, can also produce increases in cerebral blood flow (Wade and Brown, 1988).

Poiseuille's Law and Flow Through Bifurcations

In this section the effects of arterial bifurcations and artery length and radius on blood flow will be discussed. These concepts will be applied to blood flow in the cerebral arteries (and to the pathogenesis of RLS and PLMS) in the next major section.

The flow (F) of blood through arteries and veins, like the flow of any fluid in a tube, is affected by several variables. These include the length (L) and radius (r) of the artery (or tube), the viscosity (η) of the blood (or fluid), and the difference in pressure between the two ends of the artery (or tube). Poiseuille's law is a formula which describes how these variables affect the amount of flow. This formula is

usually cited in most physiology texts (e.g. Ganong, 1995, p. 530), and is written as follows:

$$F = (P_A - P_B) \times (\pi/8) \times (1/\eta) \times (r^4/L)$$

where $P_A - P_B$ is the difference in pressure between the proximal and distal ends of the tube.

Flow is also equal to the pressure difference ($P_A - P_B$) divided by the resistance to flow (R) (Ganong, 1995, p. 531). Thus, resistance to flow (R) can also be described in terms of the variables mentioned above; that is, the length and radius of the artery (or tube) and the viscosity of the blood (or fluid). The equation which describes how these variables affect resistance is written as follows (Ganong, 1995, p. 531):

$$R = 8\eta L/\pi r^4.$$

It can be seen from this equation that resistance to blood flow is directly proportional to the length (L) of an artery and inversely proportional to fourth power of the radius of the artery (r^4). This means that small increases in the radius of an artery greatly reduce the resistance to flow, while small decreases in the radius greatly increase the resistance to flow.

Blood flow in arteries is laminar under normal conditions (Ganong, 1995, p. 530). Laminar flow refers to

the observation that blood flows in a straight line fashion, but with different velocities in different concentric "layers" or lamina within an artery. For example, the flow velocity is highest in the middle of the artery, and lowest (approaching zero) at the artery wall. The lamina closest to the wall of the artery is referred to as the boundary layer. A variety of factors can cause disruptions or turbulence in the normal laminar flow. These include increased flow velocity, increased vessel diameter, increased fluid density, and decreased blood viscosity. The Reynolds number is a ratio which indicates how likely turbulence is to occur. It takes into account the variables listed above, and is computed as follows:

$$Re = \rho DV/\eta$$

where ρ equals the density of the fluid, D equals the diameter of the tube, V equals the flow velocity, and η equals the viscosity of the fluid. Under normal conditions in straight vessels, turbulent flow usually does not occur until the Reynolds number reaches about 2300, a value which is usually not attained (Nichols and O'Rourke, 1990).

Turbulent flow and other types of non-laminar flow such as eddying commonly occur at arterial bends and

bifurcations (Fox and Hugh, 1966; Friedman, Deters, Mark, Bargeron, and Hutchins, 1983; Roach, 1977). The turbulent flow and eddying that occurs at these sites has been shown to produce regions of both high and low shear stress, and both high and low shear stress have been implicated in the genesis and progression of atherosclerosis (Friedman et al, 1983; Gutstein, Schneck, and Marks, 1968; Nichols and O'Rourke, 1990; Roach, 1977). Friedman et al. (1983) performed flow studies in casts of human aortas, and demonstrated that individual differences in arterial geometry could account for the variations in shear stress that were observed. Roach and her colleagues proposed that turbulent flow and points of increased shear stress at bifurcations in the Circle of Willis could lead to the development and progression of cerebral aneurysms and cerebral atherosclerosis (Roach, 1977; Roach, Scott, and Ferguson, 1972).

The turbulence and eddying that occurs at bifurcations also impedes the flow of blood through these regions by decreasing the area available for blood flow. This has been clearly demonstrated in studies which have shown that blood flows around, rather than through, the regions of eddying and turbulence (Crowe and Krovetz, 1966; Fox and Hugh, 1966).

There are several geometrical features of bifurcations that appear to increase the probability that turbulence and eddying will occur. These include branching asymmetry and increases in the angle of the bifurcation (Crowe and Krovetz, 1972; Roach, Scott, and Ferguson, 1972). Because these factors affect turbulence, they also affect flow rates. Crowe and Krovetz (1972) demonstrated that flow rates in arterial branches were greater in symmetrical "Y" type bifurcations than in the daughter branches of asymmetrical "parent vessel/daughter vessel" bifurcations, a finding which indicated that more turbulence and flow disruption occurred in the asymetrical bifurcations. Crowe and Krovetz (1972) also showed that as the angle of bifurcation in an asymetrical bifurcation increases, the flow rate through the "daughter vessel" decreases. Similarly, Roach et al. (1972) showed that the critical Reynolds number (the Reynolds number at which turbulence develops) decreased as the angle of bifurcation increased, although it should be noted that these results were for symetrical "Y" type bifurcations. Taken together, these results suggest that individual differences in arterial geometry can affect both flow rate and shear stress. Friedman et al. (1983) suggested that

such individual differences might represent a risk factor for the development of coronary atherosclerosis.

Cerebral Blood Flow During Sleep

A fairly large number of studies have investigated cerebral blood flow during normal human sleep and wakefulness. Overall, the results are very consistent with respect to global cerebral blood flow levels during the different sleep-wake states. During non-REM sleep there is a progressive decrease in total cerebral blood flow with the lowest levels being achieved in slow-wave sleep (SWS)(Masden et al., 1991; Sakai, Meyer, Karacan, Derman, and Yamamoto, 1980; Townsend, Prinz, and Obrist, 1973). The average decrease in cerebral blood flow during SWS (as compared to wakefulness) in these studies was 25% in the Masden et al. study, 28% in the Sakai et al. study, and 10% in the Townsend et al. study. All of these studies used the ^{133}Xe inhalation technique to assess cerebral blood flow. During REM sleep, total cerebral blood flow was either not significantly different from levels observed during wakefulness (Masden et al., 1991) or was higher than that observed during wakefulness (Sakai et al., 1980; Townsend et al., 1973).

Similar results have been reported for cerebral metabolic rate as assessed by positron emission tomography

of [^{18}F]2-fluoro-2-deoxy-D-glucose uptake. For example, Buchsbaum et al. (1989) reported that glucose uptake decreased by 23% during NREM sleep as compared to wakefulness, while there was only a small non-significant decrease during REM sleep. Maquet et al. (1990) found a 43.8% percent decrease in glucose uptake during SWS as compared to wakefulness, and a small non-significant increase during REM sleep.

The similar pattern of results obtained for cerebral blood flow and cerebral glucose utilization have been cited as evidence that flow-metabolism coupling of cerebral blood flow persists throughout the sleep-wake cycle (Masden et al., 1991). However, there are a number of findings which suggest that cerebral blood flow and cerebral metabolism are not tightly coupled during sleep, particularly during non-REM sleep. The most important of these is that end-tidal CO_2 levels increase during non-REM sleep as compared to wakefulness (Sakai et al., 1980; Townsend et al., 1973). If flow-metabolism coupling persisted during non-REM sleep, then one would expect an increase in cerebral blood flow in response to these increased CO_2 levels. The decreased cerebral blood flow in spite of these increased CO_2 levels suggests that there is a decrease in cerebral vasomotor responsiveness to CO_2

during non-REM sleep (Sakai et al., 1980). Results similar to these were obtained in a recent study which near-infrared spectroscopy (NIRS) was used to assess cerebral oxygenation and blood flow accross an entire night in seven normal healthy subjects (Hoshi, Mizukami, and Tamura, 1994). NIRS is a technique in which cerebral oxyhemoglobin, deoxyhemoglobin, and total hemoglobin can be measured. The total hemoglobin measurement is thought to correlate well with total blood volume (Brazy, 1991), and as such, reflects total cerebral blood flow. The study by Hoshi et al. showed that oxyhemoglobin decreased during non-REM sleep, and returned to waking levels during REM sleep. Despite the decrease in cerebral oxygen levels, total blood flow (as assessed by the total hemoglobin measurement) decreased during non-REM sleep. Hoshi et al. (1994, p. 257) concluded that their results suggested that "the flow-metabolic coupling mechanism is reset to a new level during sleep."

A similar conclusion was reached in another recent study in which transcranial Doppler sonography was used to assess cerebral blood flow velocity across the entire night (Hajak et al., 1994). As noted earlier, cerebral blood flow velocity correlates fairly well with cerebral blood flow volume. Hajak et al. found that cerebral blood

flow velocity decreased during progressively during non-REM sleep (as compared to pre-sleep baseline values), and increased during REM relative to the preceding non-REM sleep values. These results were similar to those obtained by the authors cited above who used the ^{133}Xe technique to assess cerebral blood flow. However, Hajak et al. observed several things which suggested that flow-metabolism coupling was not present during sleep. First, there was a general trend for flow velocity to decrease across the night. For example, flow velocity values for both non-REM and REM sleep were found to decrease as compared to those seen in earlier sleep cycles. Second, during spontaneous or provoked arousals, there was often no response in flow velocity, and in many subjects there was actually a decrease in flow velocity in response to the arousal. Finally, upon awakening in the morning, there was often a delay of up to 30 minutes before flow velocity returned to the pre-sleep baseline level. These findings led Hajak et al. (1994, p. 11) to conclude that "these results imply an uncoupling between cerebral electrical activity and cerebral perfusion during sleep...".

Like Hajak et al., Hoshi et al. (1994) also used auditory stimulation to study the cerebral blood flow

response to arousal during sleep. Hoshi et al. observed large disproportionate increases in total hemoglobin during arousals produced during REM sleep, and relatively smaller increases during non-REM sleep. They noted that the large arousal-induced increases in blood flow during REM sleep were qualitatively similar to those observed by other authors during wakefulness in response to somatosensory stimulation (e.g. Fox and Raichle, 1986), while the arousal-induced increases in blood flow during non-REM sleep were much more subdued.

The findings suggestive of flow-metabolism uncoupling during non-REM sleep has led several of the authors in the studies cited above to conclude that cerebral blood flow during sleep may be regulated primarily by central neurogenic mechanisms rather than by local flow-metabolism coupling (Hajak et al, 1994; Hoshi et al., 1994, Sakai et al., 1980; Townsend et al., 1973). As it will be noted in the section to follow, these changes in the regulation of cerebral blood flow across the sleep-wake cycle can potentially explain the sleep-related appearance of both RLS and PLMS.

Periodic Cerebral Ischemia: A New Theory for the Pathogenesis of Restless Legs Syndrome and Periodic Limb Movements in Sleep

Anatomical Considerations Regarding the Paresthesia in RLS

As reviewed above, the pathogenic theory of RLS that has the best support is the reduced peripheral blood flow theory. However, because the same arteries that supply blood to the lower legs also supply the feet (Moore, 1985, p. 432), this theory cannot explain the restriction of the paresthesia in RLS to the lower legs. Despite this, there is much evidence to suggest that some impairment in circulation is present in RLS and PLMS (e.g. the prevalence data, most of the treatment data, the transient nature of the symptoms). Thus, it is reasonable to assume that the paresthesia in RLS is caused by a transient "functional" lesion of neurons mediating somatosensation in the legs, and further that this transient "functional" lesion is caused by ischemia (and/or hypercapnia) secondary to insufficient blood flow somewhere in the nervous system.

If this assumption is taken as an initial working hypothesis, the next question that arises is which neurons that mediate somatosensation in the lower legs undergo this reduction in blood flow. Because there are only four levels of neurons in the somatosensory pathway (for

proprioception and light touch), there are a limited number of possible answers to this question. The primary or first order sensory neurons in this pathway have their cell bodies in the dorsal root ganglion of lumbar and sacral regions of the spinal cord (Carpenter, 1991, pp. 75-77). The peripheral processes of these neurons form the peripheral nerves, while the central processes (axons) ascend in the fasiculus gracilis of the dorsal funiculus of the spinal cord. These axons synapse on second order neurons in the ipsilateral nucleus gracilis of the medulla. The second order neurons in the nucleus gracilis send axons to the ventral posterolateral nucleus of the contralateral thalamus via the medial lemniscus. The third order neurons in the ventral posterolateral nucleus of the thalamus then project to fourth order neurons in the leg area of the somatosensory cortex of the ipsilateral cerebral hemisphere. This area of the somatosensory cortex is located almost entirely within the longitudinal fissure dorsal to the cingulate gyrus (see Carpenter, 1991; Figure 13.13, p. 404). Thus, to produce the paresthesia in RLS, a reduction in blood flow would probably have to occur in one of the following areas: the fasiculus gracilis in the spinal cord, the nucleus gracilis in the medulla, the ventral posterolateral

nucleus in the thalamus, and/or the leg area of the somatosensory cortex.

These possibilities can be narrowed down further if PLMs are taken into account. Recall that Smith (1985) observed that PLMs appear to be spontaneously occurring Babinski responses. As noted earlier, Babinski responses occur only when pyramidal tract damage is present (van Gijn, 1978; 1995). Thus, like the paresthesia in RLS, PLMs may also be caused by a ischemia-induced "functional" lesion, but in the case of PLMs, the lesion would need to be somewhere within the pyramidal tract (and it would need to occur periodically). A large percentage of the cell bodies of axons that form the pyramidal tracts are located within the motor and premotor areas of the frontal cortex; however, many other pyramidal tract neurons are located in the somatosensory cortex on the post-central gyrus of the parietal lobe (Carpenter, 1991, pp. 94-96). Thus, a "functional" lesion of the leg area of the somatosensory cortex could cause both the waking paresthesia of RLS, and the PLMs that are seen in these patients during sleep.

If the blood supply to this area, and to the other areas listed above, is examined it becomes clear that the most likely site of the reduced blood flow responsible for

the paresthesia in RLS (and for PLMs) is in the leg area of the somatosensory cortex.

Beginning first with the fasiculus gracilis, it can be seen from Gilman and Newman (1992; Figure 27, p. 93) that this area is supplied by branches arising from the posterior spinal arteries. However, the posterior spinal arteries also supply the fasiculus cuneatus which mediates somatosensation in the trunk and upper extremities, so it is unlikely that reduced flow in these arteries could produce a paresthesia restricted primarily to the lower legs. Moreover, the pyramidal tracts descend in the lateral funiculus, which is supplied by the anterior spinal artery (see Gilman and Newman, 1992; Figure 27). Thus, in order to account for both RLS and PLMS via a spinal blood flow mechanism, one would have to postulate reduced flow in all of the major spinal arteries. If this did happen, it seems likely that the symptoms produced would be restricted to the dermatomes that were affected, and would include symptoms in addition to those typically reported in RLS (e.g. numbness, pain, tingling). However, as noted earlier, the anatomical distribution of the paresthesia in RLS does not match any of the body areas supplied by any dermatome.

If RLS were due to reduced blood flow in the region of the nucleus gracilis (which is located in the dorsal medulla), then the artery most likely to be involved would be the posterior inferior cerebellar artery. In addition to supplying the cerebellum, this artery supplies parts of the medulla (Carpenter, 1991; see Figure 14.3, p. 439). However, the pyramidal tracts (which are located in the ventral medulla) are supplied by branches from the anterior spinal artery near its point of origin. Thus, to account for both RLS and PLMS via reduced blood flow to the medulla, one would have to postulate reduced blood flow in at least two arteries. Moreover, the regions of the medulla supplied by these arteries are very likely to include other body areas in addition to the lower legs.

If the paresthesia in RLS was due to reduced blood flow in the ventral posterolateral nucleus of the thalamus, then the arteries most likely to be involved would be the anterior choroidal artery (which arises from the anterior cerebral artery) and the thalamogeniculate arteries (which arise from the posterior cerebral artery; see Carpenter, 1991; Figures 14.9 and 14.10, p. 447). However, the ventral posterolateral nucleus of the thalamus is a relatively small nucleus which also mediates somatosensation in the trunk and upper limbs. Thus, it

seems unlikely that reduced blood flow in this area could produce a paresthesia restricted primarily to the lower legs. In regards to PLMS, it can be seen from Carpenter (1991; Figure 14.10) that the pyramidal tracts descend near the thalamus in the internal capsule. However, it can also be seen in Carpenter (1991; Figure 14.10) that the internal capsule is supplied by both the anterior choroidal artery and by other branches from the middle cerebral artery. Therefore, in order to account for both RLS and PLMS via reduced blood flow in the region of the thalamus and internal capsule, one would have to postulate that blood flow would be reduced in several arteries.

The course of the anterior cerebral artery and its major branches are best seen in mid-sagittal sections of the brain (e.g. see Carpenter, 1991; Figure 14.5, p. 442), while the territory perfused by this artery is best seen in coronal and mid-sagittal sections (see Gilman and Newman, 1992; Figure 76, p. 267, for a coronal section showing the territory perfused by the anterior cerebral artery). If one compares the somatosensory cortex for the leg (see Carpenter, 1991, Figure 13.13) with mid-sagittal and coronal views of the territory perfused by the anterior cerebral artery, it can be seen that the distal territory of the callosomarginal branch of the anterior

cerebral artery roughly corresponds to the somatosensory area for the legs. The more proximal territory of the callosomarginal branch of the anterior cerebral artery corresponds to the motor area for the legs. Thus, if blood flow were preferentially reduced in the callosomarginal branch of the anterior cerebral artery, one would expect to see symptoms of leg paresthesias, and in addition, one would expect that this reduced flow might produce a transient "functional" pyramidal tract lesion.

A careful examination of figures presented in Carpenter (1991; Figure 13.13) and Gilman and Newman (1992; Figure 76) shows that the territory perfused by the callosomarginal branch of the anterior cerebral artery includes the entire lower extremity, including the feet. Thus, the familiar question of why the paresthesias in RLS occur primarily in the lower legs but not the feet arises again. The answer to this question can be found in the data presented by Van der Zwan and Hillen (1990). These authors demonstrated that the territories perfused by the major cerebral arteries were dynamic, and could shift (i.e. contract or expand) if the perfusion pressure suddenly dropped in one of the major arteries. Thus, if blood flow was preferentially reduced in the callosomarginal branch of the anterior artery, one could

expect that the core area of the territory perfused by this artery would experience the greatest reduction in blood flow and the most severe ischemia. An examination of the figures mentioned above (Carpenter, 1991, Figure 13.13; Gilman and Newman, 1992, Figure 76) shows that the core area perfused by the callosomarginal branch of the anterior cerebral artery roughly corresponds to the lower legs and does not include the somatosensory cortex for the feet or lower torso/upper thigh. Therefore, reduced blood flow in this artery could explain why the paresthesia in RLS is restricted to the lower legs excluding the feet.

In summary, if one assumes that the basic pathology of both RLS and PLMS involves some impairment of blood flow, then it can be argued that the most likely artery and location for this impairment in blood flow is the distal territory perfused by the callosomarginal branch of the anterior cerebral artery. This argument forms the basis of the periodic cerebral ischemia theory of RLS and PLMS.

Some Additional Questions

Even if one accepts the argument presented above, several additional questions or problems arise as to how such a reduction in blood flow might occur. The first of these questions concerns the issue of how blood flow could

be preferentially reduced in a single branch of one of the three major cerebral arteries. The second question concerns the issue of how such an abnormal decrease in blood flow could continue, to an extent sufficient to produce paresthesia, without eliciting a rapid compensatory increase in cerebral blood flow. The third question concerns the issue of why such changes apparently begin during wakefulness in RLS patients, but do not begin until sleep is achieved in PLMS patients. The fourth and final question concerns the periodicity of PLMs both during wakefulness (in RLS patients) and sleep (in PLMS patients).

The first question mentioned above is the most important. The Periodic Cerebral Ischemia theory of RLS and PLMS asserts, as argued in the section above, that both disorders are caused by periodic reductions in cerebral blood flow that are largest in the distal territory perfused by the callosomarginal branches of the anterior cerebral arteries. The answer to the question of how this could happen can be found in the information presented earlier about the effects of bifurcations and artery length and radius on resistance to blood flow: both increasing the length of an artery and decreasing its radius result in an increased resistance to blood flow.

An examination of Figure 14.5 in Carpenter (1991) shows that the anterior cerebral artery and its callosomarginal branch are relatively long arteries whose most distal territories lie a long way from the point of origin of the anterior cerebral artery. Although it is not depicted as such in Carpenter's figure, the anterior cerebral artery has the smallest radius of the three major cerebral arteries (e.g. see Moore, 1985, Figure 7.77, p. 880). The nature of the bifurcations present in the anterior cerebral artery and its branches also contribute to the proposed preferential reduction in blood flow in the callosomarginal branch of the anterior cerebral artery. Recall that the amount of blood flow into the daughter branch of an asymmetrical bifurcation is lower than the flow in the main trunk (Crowe and Krovetz, 1972). Moreover, two studies have shown that as the angle of bifurcation increases, the region of turbulence or probability of turbulence in the daughter branch increases, with a corresponding decrease in total flow through the daughter branch (Crowe and Krovetz, 1972; Roach et al., 1972). An examination of figures presented in Carpenter (1991; Figure 14.3 and 14.5) shows that the anterior cerebral artery has several asymmetrical bifurcations. The first of these is its point of origin

where it branches off as a daughter branch from the internal carotid/middle cerebral artery. The second bifurcation occurs where the anterior communicating artery branches off from the anterior artery. Finally, the callosomarginal branch is a daughter branch of the anterior cerebral artery, and the callosomarginal branch has several bifurcations prior to terminating in its most distal territory. The combination of these bifurcations and the long length and small radius of the anterior cerebral artery and its branches could thus result in a relative reduction in blood flow that is greatest in the distal territory perfused by the callosomarginal branch of the anterior artery. Another likely possibility that may contribute to the development of both RLS and PLMS in certain individuals is that there is probably a significant variation among individuals in the three factors listed above: length and radius of the anterior cerebral artery, and the angle of its bifurcations. Thus, certain individuals might be at an increased risk of developing RLS and/or PLMS because of their individual arterial geometry.

The second question concerns the issue of why the proposed reduction in blood flow and subsequent ischemia are not corrected before they proceed to an extent

sufficient to produce RLS and PLMS symptoms. The answer to this question can be found in the data presented above which suggests that flow-metabolism coupling and cerebral vasomotor responsiveness to CO_2 are greatly reduced during non-REM sleep (Hajak et al., 1994; Hoshi et al., 1994; Sakai et al., 1980; Townsend et al., 1973). All of the authors in these four studies suggested that cerebral blood flow during sleep was regulated primarily by central neurogenic mechanisms rather than by flow-metabolism coupling. Thus, the presence of ischemia in a relatively small area of the cerebral cortex (one not involved in the regulation of cerebral blood flow during sleep) might not be sufficient to provoke a compensatory increase in regional or global cerebral blood flow.

In regards to the third question listed above, the Periodic Cerebral Ischemia theory of RLS and PLMS proposes that the same pathology operates in both disorders, with the major difference between the two disorders being that the abnormalities of cerebral blood flow (i.e. shift from flow-metabolism coupling to central neurogenic control with high amplitude B-wave activity) begin during wakefulness in RLS, but not until sleep is achieved in PLMS. The shift in how cerebral blood flow is regulated in RLS is proposed to occur when triggered by prolonged

motor inactivity (perhaps with some associated drowsiness) rather than by sleep itself. There is some limited evidence to support this assertion. First, Montplaisir et al. (1994) found periodic slowing in the EEG of RLS patients during a Forced Immobilization Task administered while the patients were awake. While this is not direct evidence of B-wave activity, the close association of CAP and B-wave activity suggests that B-wave activity may very well have been present. Second, Oakson and Steriade (1982) found that mesencephalic reticular formation neurons had periodic oscillations in their firing rates with periods varying between eight and twelve seconds. The pertinent finding of interest in their study was that these oscillations occurred only during non-REM sleep and during quiet wakefulness without movement. Finally, at least two studies which used transcranial Doppler sonography to test for the presence of B-waves in normal subjects found that these oscillations were present during wakefulness (Diehl et al., 1991; Mautner et al., 1989). Thus, it is not unreasonable to posit that a shift in the regulation of cerebral blood flow from a regional flow-metabolic coupling mechanism to a central neurogenic mechanism (with B-wave activity) can be precipitated by prolonged motor inactivity during wakefulness.

The fourth question concerns the periodicity of PLMs, and a possible periodicity of RLS sensory symptoms. The Periodic Cerebral Ischemia theory of RLS and PLMS proposes that high amplitude B-waves during prolonged motor inactivity and non-REM sleep are a constant feature of the cerebral hemodynamics of RLS and PLMS patients. This oscillation in total cerebral blood flow (coupled with the anatomical and geometrical features peculiar to the anterior cerebral artery) causes a periodic cerebral ischemia that is greatest in magnitude in the distal territory of the callosomarginal branch of the anterior cerebral artery. This periodic ischemia produces both the sensory and motor symptoms of RLS (which are predicted to be periodic in nature), and a periodic "functional" lesion of the pyramidal tracts that is sufficient to cause the spontaneous occurrence of a Babinski response (i.e. to cause a PLM). As noted earlier, several investigators have found that the leg movements that occur during wakefulness in RLS patients may be periodic (e.g. Montplaisir et al., 1994). One prediction of this theory that has not been directly tested is that the paresthesias in RLS should occur in a periodic fashion similar to PLMs. This hypothesis actually does receive some support from the study of Pelletier et al. (1992), which found that

sensory events in RLS patients were almost always accompanied by waking PLMs. Unfortunately, no specific data regarding the periodicity and duration of the sensory events experienced by the subjects were presented by these authors.

Although it is proposed that high amplitude B-wave activity is one of primary abnormalities in RLS/PLMS, another possibility is that total cerebral blood flow is lower (perhaps due to excessive vasoconstriction), while B-wave amplitude is the same. If this were the case, then periodic cerebral ischemia would still occur at the B-wave troughs. Although this is possible, it seems unlikely for several reasons. First, during wakefulness, total cerebral blood flow is tightly regulated, and the brain is very sensitive to hypoxia (e.g. unconsciousness results in as little as ten seconds if the blood supply to the brain is cut off, Ganong, 1995, p. 564). Second, if total blood flow were abnormally low, one would probably see a variety of neurological and cognitive symptoms suggestive of ischemia. Third, studies of B-wave activity in normal subjects (Diehl et al., 1991; Droste et al., 1993; Newell et al., 1992) have found large individual differences in B-wave amplitude (e.g. from ± 10 to 30 percent of the mean flow velocity), so it has already been demonstrated that

some individuals have B-waves that are much larger in amplitude than others. Thus, it is proposed that there are two pathologies in RLS and PLMS patients which contribute to producing a periodic ischemia which is greatest in the distal territory of the callcsomarginal branch of the anterior cerebral artery: 1) abnormally large amplitude B-waves, and 2) abnormal structural geometry in the anterior cerebral artery and its branches.

The Periodic Cerebral Ischemia Theory of RLS and PLMS

The arguments presented above can be briefly summarized into the following statement of the Periodic Cerebral Ischemia theory of RLS and PLMS.

It is proposed that both RLS and PLMS are caused by a combination of sleep-related changes in the regulation of cerebral blood flow and the unique anatomical features of the anterior cerebral artery and its branches. These factors combine to produce a periodic cerebral ischemia which is greatest in magnitude in the distal territory perfused by the callosomarginal branch of the anterior cerebral artery. This cortical territory contains the somatosensory and motor cortices for the legs; the central core of this territory overlaps well with bodily areas in which RLS paresthesias most commonly occur (i.e. the lower legs excluding the feet). The sleep-related changes in

cerebral blood flow, referred to above, include a shift from a local flow-metabolism coupling control mechanism to a central neurogenic control mechanism. Associated with the central neurogenic control of cerebral blood flow are high amplitude B-waves (i.e. oscillations in total cerebral blood volume). These B-waves are proposed to be significantly higher in amplitude among persons who have RLS and PLMS than in those who do not, and to begin during inactive wakefulness in RLS patients and after sleep onset in patients with PLMS alone.

The periodic ischemia in the motor and somatosensory cortices of the leg area occurs during both wakefulness (in RLS patients) and non-REM sleep (in PLMS patients and most RLS patients). During wakefulness, this periodic ischemia produces the waking sensory and motor symptoms of RLS. During non-REM sleep, the ischemia produces a periodic "functional lesion" of the pyramidal tracts which results in the spontaneous occurrence of a Babinski response. This Babinski response equates to the observed PLM. PLMs are not generally seen in REM sleep for two reasons: first, because of the generalized muscle atonia seen in this sleep stage (Kanamori et al., 1980), and second, because total cerebral blood flow during REM sleep

is similar to that seen in wakefulness (e.g. Townsend et al., 1973).

As was done for the existing major pathogenic theories of RLS and PLMS presented earlier, an attempt will be made to see how well the Periodic Cerebral Ischemia of RLS and PLMS can account for the major features of both disorders.

The restriction of paresthesias in RLS to the lower legs excluding the feet can be explained by the observation that the territories perfused by the cerebral arteries are dynamic and can contract when the perfusion pressure falls. It is suggested that this occurs in the callosomarginal branch of the anterior cerebral artery, with the result that only the central core of this territory (which includes the somatosensory areas for the lower legs but not the feet) is affected.

The precipitation of RLS symptoms by inactivity can be explained by the observation that prolonged inactivity may trigger a shift in how cerebral blood flow is regulated (from a local flow-metabolic coupling mechanism to a central neurogenic control mechanism). Associated with this shift to a central neurogenic control of cerebral blood flow are high amplitude B-waves and a

reduced cerebral vasomotor responsiveness to vasodilator metabolites, including CO_2.

The relief of RLS symptoms by vigorous activity can be explained by suggesting that such activity causes a shift from the central neurogenic control of cerebral blood flow back to the flow-metabolism coupling control seen in normal active wakefulness. The vigorous leg activity in particular causes increased metabolism in the sensory and motor cortices for the legs, with a subsequent increase in cerebral blood flow to this region. This increased blood flow alleviates the ischemia that was causing the symptoms.

The circadian and sleep-related appearance of RLS and PLMS can be explained by suggesting that there is a normal tendency for the control of cerebral blood flow to shift to a central neurogenic control mechanism in the evening and during sleep.

The higher than normal prevalence of RLS and PLMS in the various patient groups mentioned above can be explained by the observation that most of these disorders are associated with either anemia or circulatory impairments. Thus, persons with these disorders already have a tendency towards insufficient oxygen delivery to the body and brain.

The effectiveness of the various drugs reviewed above in treating RLS and PLMS can be explained by the observations that several of them appear to improve circulation, including cerebral blood flow, directly (e.g. correction of anemia, dextran, L-DOPA, clonidine, sclerotherapy) while others (benzodiazepines, opioids, anti-convulsants) may reduce the amplitude of B-waves by acting directly on brainstem vasomotor areas (e.g. see Haxhiu et al., 1989).

Finally, the periodicity of PLMS can be explained by the suggestion that it is high amplitude B-wave activity that underlies the generation of these movements.

The issue of treatment of RLS and PLMS deserves further comment. If the above theory is correct, then the best type of drug to treat both RLS and PLMS would clearly be some type of vasodilator. In addition, if the above theory is correct, it would suggest that the effectiveness of most of the drugs currently used to treat RLS and PLMS is the result of their hemodynamic effects. This underscores the fact that the mechanism by which these drugs exert their beneficial effects on RLS and PLMS remains unknown. Although some of these drugs do have hemodynamic effects (e.g. vasodilation in the case of L-DOPA, reduced cardiac output and peripheral vasodilation

in the case of clonidine, and reduction of B-wave amplitude in the case of some benzodiazepines), these are usually not the primary effect of these drugs. In addition, many of these drugs have significant undesirable side effects. For example, L-DOPA has been shown to cause morning rebound and daytime augmentation of symptoms in RLS patients, while clonidine and anti-convulsants may cause excessive sedation. Benzodiazepines are respiratory depressants, and as such, are contraindicated in many older patients who have sleep-related breathing disorders. Although vasodilators are not without side effects and risks, they are probably as safe or safer than many of the drugs currently being used to RLS and PLMS. In summary, if the PCI theory of RLS and PLMS can be shown to be correct, major changes in the treatment of these disorders would be indicated.

Method

Study Overview, Technical Considerations, and Hypotheses

The study described below represented an attempt to test several of the main tenets of the theory outlined above. Near infrared spectroscopy (NIRS) was utilized to assess regional cerebral hemoglobin oxygen saturation and total cerebral blood flow in RLS patients, PLMS patients, and normal controls. Studies were conducted during both wakefulness (during a Suggested Immobilization Test, SIT) and sleep. It was predicted that the RLS patients would have B-wave activity during both wakefulness and sleep, and that the amplitude of those oscillations would be greater than those in normal controls. In addition, it was predicted that the PLMS patients would have B wave activity primarily during sleep, and that the amplitudes of their B-waves during sleep would be greater than those in normal controls, but not significantly different from those in RLS patients. Although it was considered likely that both PLMS patients and normal controls would have some B-wave activity while awake (i.e. during the SIT), it was predicted that the waking B-wave amplitude in both groups would be significantly lower than that seen in the RLS patients. It was also predicted that the B-wave troughs would be associated with the sensory and motor

symptoms experienced by the RLS patients during wakefulness, and with PLMs experienced by both RLS and PLMS patients during sleep.

Before proceeding, some methodological aspects of NIRS assessment of regional cerebral oxygenation, and some specific details of the cerebral oximeter used (the Somanetics INVOS 3100A Cerebral Oximeter) need to be briefly reviewed. Several excellent reviews of NIRS and the Somanetics oximeter have been published (Dujovny, Slavin, Cui, Lewis, and Ausman, 1994; McCormick et al., 1991; Slavin et al., 1994), and the following review is based on these sources.

The wavelengths of light used in NIRS are in the near-infrared range (700 to 1100 nanometers), and easily penetrate most human tissues, including bone. The light can penetrate to a depth of several centimeters, and is absorbed by several molecules, including oxyhemoglobin, deoxyhemoglobin, and oxidized cytochrome c oxidase (McCormick et al., 1991). Both oxyhemoglobin and deoxyhemoglobin can absorb near-infrared light throughout the range of wavelengths used in NIRS (typically 700 to 900 nm), but oxyhemoglobin absorbs a greater percentage of photons at longer wavelengths (e.g. at about 900 nm), while deoxyhemoglobin absorbs a greater percentage of

photons at shorter wavelengths (e.g. at about 700 nm). At a wavelength that is referred to as the "isobestic point" (803 nm in humans), the percentage of infrared light photons absorbed by both oxyhemoglobin and deoxyhemoglobin is the same, and the amount of light absorbed will correlate with total hemoglobin. Thus, absorption at the isobestic point can be used as a measure of total blood volume. If absorption at one other wavelength is obtained (e.g. 700 nanometers), the two measures can be compared to determine how much hemoglobin is "saturated" with oxygen.

The cerebral oximeter manufactured by the Somanetics corporation (Troy, Michigan) emits near-infrared light at two wavelengths: 730 and 805 nm (Ron Widman, personal communication, June, 1997). This provides measures of total hemoglobin and deoxyhemoglobin, which are then used to compute regional oxyhemoglobin levels. The value, which is referred to as the "rSO_2 index" is then displayed on the oximeter's monitor, and can be also stored digitally, and/or sent to an analog chart recording device. The measure of total hemoglobin (i.e. absorption at the isobestic point) can also be stored digitally for later review and analysis. In addition, the oximeter has an event marker button, which allows the user to mark clinically relevant events. These marks are displayed on

the monitor, and can also be stored digitally for later review.

The light emitter and sensors used with the Somanetics oximeter are unique in that they are designed in such a way as to provide a measure of oxyhemoglobin in brain tissue only. They are specifically designed so that the rSO_2 in both brain tissue and in the overlying bone and skin can be measured. This is accomplished by the use of two sensors which are located at different distances (30 and 40 mm) from the infrared light emitter. The sensor that is closer (at 30 mm) measures predominately extracerebral rSO_2 (i.e. in the scalp, bone, and meninges), while the sensor at 40 mm measures both cerebral and extracerebral rSO_2. The value obtained from the closer sensor is then subtracted from the value obtained from the more distant sensor, yielding a measure indicative of brain tissue rSO_2.

The term "rSO_2 index" is used (by the Somanetics corporation) to indicate that the displayed value is a measure of regional oxyhemoglobin which includes both arterial and venous oxyhemoglobin. It should not be confused with the signal measured by peripheral pulse oximetry, which is a measure of arterial oxyhemoglobin saturation only. The measure obtained by pulse oximetry

is usually referred to as a SaO_2 value (the lowercase "a" indicating "arterial"). Of the total blood volume in the brain, about 70 percent is venous blood (Mchedlishvilli, 1986, pp. 55-60). Thus, the rSO_2 index, while measuring both arterial and venous oxyhemoglobin, has average values which are much closer to the oxyhemoglobin saturation of venous blood. For example, a normative study of 100 subjects by Dujovny et al. (1992) found a mean rSO_2 index of 68.6%, and a standard deviation of 5.6%. The preponderance of venous blood within the brain does not affect the ability of the Somanetics cerebral oximeter to detect cerebral hypoxia (Duncan, Ruckley, and Wildsmith, 1995; Williams, Picton, Hardy, Mortimer, and McCollum; 1994). In fact, because cerebral hypoxia often results from circulatory insufficiency rather than from abnormally low arterial oxyhemoglobin values in the blood entering the brain (e.g. such as those that might be caused by respiratory disease), the ability of NIRS to measure venous oxyhemoglobin actually enhances its ability to detect cerebral hypoxia. A large number of clinical studies have demonstrated the usefulness of NIRS in detecting cerebral hypoxia (e.g. Duncan et al., 1995; Slavin et al., 1994; Williams et al., 1994).

The sampling rate and data averaging algorithms used by the Somanetics oximeter also need be mentioned. The absorption data from both sensors is sampled at a rate of 15 Hz. Instead of being displayed and updated continuously, the oximeter collects 50 data points (which takes 3.33 seconds), and then averages these data and outputs the result to the monitor. The processing and outputting of the 50 data points takes approximately one and half seconds, and during this time the oximeter does not sample absorption data. The result is that the rSO_2 value displayed on the monitor, and all data points stored in memory, including the rSO_2 index and the total hemoglobin measure, are updated approximately once every five seconds (it should be noted that a published review of the Somanetics instrument, Dujovny et al., 1994, incorrectly stated that the instrument updates the rSO_2 value once every four seconds). This data averaging technique has the potential to slightly attenuate changes in the absorption signal such as those that might occur during oscillations of cerebral blood flow (i.e. B-waves). If oscillations are present, data averaging can also shift the peaks and troughs of the signal, although the degree of shifting is dependent on both the number of data points averaged and the period of the oscillation. However, the

data averaging window used by the Somanetics oximeter is only 3.3 seconds, which should result in only very minimal signal attenuation and shifting. The primary drawback to the Somanetics NIRS instrument (at least for purposes of the present study) is that only one data point can be obtained every five seconds.

The sensors supplied for the Somanetics oximeter are small (3.75 by 1.75 inches) and self-adhesive. They are typically placed on the forehead, and it is recommended that they not be placed over the midline in order to avoid oversampling venous blood from the mid-sagittal sinus. The recommended placement location on the forehead positions the sensor over the frontal poles--areas which are perfused predominately by the middle cerebral artery. This recommended sensor location was used in the present study. Because B-waves are thought to reflect vasomotor activity that occurs simultaneously throughout the entire cerebral arterial tree, an assumption was made in the present study, that recording rSO_2 over the frontal poles would accurately reflect the rSO_2 changes that were occurring elsewhere in the brain, including those in the distal territory of the callosomarginal branch of the anterior cerebral artery. Thus, it was assumed that the recording location used in this study would not prevent

valid tests of the experimental hypotheses from being conducted. None the less, it should be pointed out that the variables measured by the Somanetics oximeter (rSO_2 and absorption at the isobestic point) are not direct measures of intracranial pressure or blood flow velocity, and at present it is unknown if these oximetry variables correlate with variables measured by other techniques that have been used to measure B-waves (intracranial pressure, blood flow velocity).

In the present study, the rSO_2 data was sent to both a personal computer, and to a polygraph chart recorder to be displayed along with several other physiologic variables being monitored. Unfortunately, despite the use of a voltage attenuater with the polygraph, the small changes in rSO_2 that were present were essentially not visible on the chart recording. It was initially hoped that changes in the rSO_2 signal would be visible on the chart recorder so that figures showing the relationship between the rSO_2 signal and sensory/motor events could be generated from the analog chart recording.

The proposed study included three groups of subjects: one group with moderate to severe RLS, one group with PLMS only, and one group of control subjects who are without any sleep complaints. Each subject underwent a Suggested

Immobilization Test (SIT) lasting one hour, just prior to one full night of polysomnography. During the SIT, the subject was required to lie supine on the bed while attempting to remain completely still. This test was originally designed as a method of documenting the excessive motor activity that occurs in RLS patients during prolonged inactivity (Lorrain and Montplaisir, 1990). During the SIT, lower leg motor activity and several other physiologic variables were recorded polygraphically. Abnormal leg sensations were recorded by having the subjects depress a switch which placed a mark on the time line signal of the polygraph. The polysomnographic recordings included measurements of cerebral oximetry (rSO_2), EEG activity, eye movements (electrooculogram, EOG), submental electromyogram (smEMG) activity, air flow, respiratory effort, electrocardiogram, and muscle activity from the anterior tibialis muscles (atEMG).

The following experimental hypotheses were tested:

1) It was predicted that the RLS patients would have significantly greater sensory and motor indices (number of events per hour) during the SIT than the PLMS subjects and the control subjects, while no significant difference between the PLMS and control subjects were expected.

2) It was predicted that the RLS and PLMS patients would have significantly higher PLM indices than the control subjects, and more disturbed sleep as indicated by the

following: Lower sleep efficiency, lower slow wave sleep percent, higher Stage 1 percent, more sleep stage changes per hour of sleep, more Stage 1 periods per hour of sleep, and more transient arousals per hour of sleep (the sum of the spontaneous and PLM arousal indices was used). In addition it was predicted that the RLS patients would have significantly less total bed time during the recording period, and a significantly longer sleep onset latency, than the PLMS and control subjects.

3) It was predicted that the abnormal leg sensations in RLS patients during the SIT would be brief (averaging less than five seconds in duration) and periodic (at least 80 percent of the total number would to conform to the scoring criteria currently in use for PLMS).

4) It was predicted that the mean peak to trough amplitude of the B-wave activity (in the rSO_2 index) in RLS patients during periods where symptoms were present during the SIT would be significantly greater than the mean amplitude of B-wave activity occurring in normal subjects and PLMS patients during the SIT. The B-wave amplitudes between the PLMS and control groups were not expected to differ significantly.

5) It was predicted that the mean peak to trough amplitude of the B-wave activity in RLS and PLMS patients during sleep (when PLMs were present) would be significantly greater than the mean peak to trough amplitude of B-wave activity during sleep in the normal control subjects. The B-wave amplitudes between the RLS and PLMS groups were not expected to differ significantly.

6) It was predicted that the sensory and motor events in RLS patients during the SIT would occur at the rSO_2 B-wave troughs, and that the average rSO_2 values occurring at the beginning of the sensory and motor events would be significantly lower than the average B-wave trough rSO_2 values (or average rSO_2 values if no B-waves were present) of the PLMS and normal control subjects. Similarly, it was predicted PLMs during sleep would occur at rSO_2 B-wave troughs, and that the average rSO_2 values at the beginning of PLMs in the RLS and PLMS subjects would be significantly lower than the average B-wave trough rSO_2 values (or average rSO_2 values if no B-waves were present) of the normal controls during sleep.

7) It was predicted that in RLS and PLMS subjects, the average rSO_2 values occurring at the beginning of each sensory and motor event during the SIT, and at the beginning of each PLM during sleep, would be significantly lower than the average rSO_2 values occurring at the next peak of the B-wave cycle (or the highest value in the next 40 seconds if no B-waves were present).

8) It was predicted that in RLS and PLMS patients, a significantly greater percentage of sensory and motor events during the SIT, and PLMs during sleep, would occur at a single point in the B-wave cycle (i.e. trough, peak, ascending limb, descending limb) rather than occurring randomly in the cycle.

Subjects

Subjects were nine patients with moderate to severe RLS (five males, four females, mean age 50.3 years), six patients with PLMS (four males, two females, mean age 49.2 years), and eleven normal controls (five males, six females, mean age 46.2 years) who were without clinically significant sleep complaints or abnormal sleep/wake cycles. Two additional subjects were run, but excluded from the data analyses; one because of unacceptably poor signal quality readings in the rSO_2 data for most of the night, and one because she could not be classified as either a PLMS or control subject based on the criteria described below. In addition, the SIT data from one control subject were not used because he fell asleep repeatedly during the SIT. There were no significant differences among the groups in age ($F_{2, 23} = 0.41$, $p = .67$).

In order to be included in the RLS patient group, subjects had meet the International RLS Study Group criteria for RLS (Walters, 1995). Briefly, they had to report all four of the following characteristics: 1) A desire to move the limbs, usually associated with paresthesias, 2) Motor restlessness, 3)Symptoms worse at rest with at least partial relief by activity, and 4) Symptoms had to be worse in the evening and/or night. A modification of the ASDA severity criteria for RLS (D.C.S.C., 1990) was used to define "severe" RLS. Specifically, RLS patients were included only if they meet the following modification of the D.C.S.C. criteria for "severe" RLS: 1) symptoms cause significant delay of sleep onset, moderate disruption of sleep, and mild impairment of daytime functions, and 2) symptoms occur three or more times a week. Significant delay of sleep onset was defined as a sleep onset latency of thirty minutes or greater during nights when symptoms were present, while moderate disruption of sleep was defined as a total sleep time of six and half hours or less during nights when symptoms were present or a self-report of moderately disturbed sleep. This modification of the severity criteria was based on clinical experience which has shown that many patients have symptoms that are

relatively frequent while being moderate in severity. Seven of the nine RLS patients had been previously diagnosed with RLS by a physician, and six of these were being treated at the time they entered the study (three with L-Dopa, two with clonazepam, and one with propoxyphene). As per the study protocol, these subjects did not take their RLS medications on the day (and night) they participated in the study. All of these subjects obtained written approval from their physician to participate in the study, and to abstain from their medication for 24 hours. Phone interviews and a 42-item self-report questionnaire called the "Restless Legs Questionnaire" (Hurry, unpublished; see Appendix 1) were used to assist in making a probable diagnosis of RLS in the two patients who had not formally diagnosed with RLS, and also to confirm the diagnosis in those who had been previously diagnosed. Seven of the nine RLS subjects had PLMS while asleep.

It was initially proposed to require PLMS subjects to have ten or more PLMs per hour of sleep. However, because of the difficulty in finding and recruiting these subjects, one subject with a PLMi of seven was included (the other five subjects all had a PLMi of ten or more). PLMs were recorded and scored according to standard

criteria (ASDA Atlas Task Force, 1993). Briefly, each movement had to be a 0.5 to 5.0 second burst of anterior tibialis EMG activity that was part of a sequence of at least four such movements, each of which were separated by more than 5 but less than 90 seconds. In order to be certain that only unambiguous PLMs were used in the data analyses, only those PLMs which occurred in a series of at least ten PLMs were used in the data analyses. All six of the PLMS subjects were recruited as normal controls; none had any complaint of insomnia or non-restorative sleep.

The normal control subjects did not have any significant sleep disturbances or excessive daytime sleepiness as indicated by their responses on the screening questionnaires listed below. They also reported having relatively normal and typical sleep/wake cycles; e.g., bedtimes after sunset, wake times soon before or after sunrise daily, with no more than two hours variation each day. Three of the control subjects had PLM indices of five or more (5.5, 5.6, and 6.0), but were included as controls because none of their movements occurred in a series of at least ten movements. Another subject who had a PLMi of 14.8 with no movements occurring in a series of least ten movements was excluded from the study because

the highly variable IMIs of her movements cast doubt on whether or not they were actually PLMs.

Four subjects (one with RLS, two with PLMS, and one control) had an Apnea plus Hypopnea Index of ten or more (the AHIs were 10, 14, 16, and 22, all indicative of a mild or moderate disorder). In two of these subjects, the events occurred primarily in supine REM, in one subject the events occurred primarily in REM regardless of sleep position, and in one subject the events occurred primarily near sleep onset regardless of sleep position. Because the respiratory events in these subjects were not related to any observed PLMs, and because sufficient sleep time free from respiratory events occurred in these subjects, all four of these subjects were included in the data analyses.

As part of the subject screening and selection process, all subjects (patients and controls) completed the Sleep Disorders Inventory, a 64-item questionnaire used to screen for a range of sleep disorders (Waters, unpublished; see Appendix 1). Each subject was also required to complete two weeks each of an 11-item Sleep Diary (filled out each morning; modified from Lacks, 1987), and a 15-item Daily Sleepiness Scale-Form D (Hurry and Waters, 1996; see Appendix 1) which was filled out

each evening. These measures were used to rule out subjects with suspected sleep apnea syndromes, psychophysiological insomnia, narcolepsy, and other sleep disorders.

RLS patients were recruited by several methods, including a mention of the study in a local (Baton Rouge, LA) newspaper editorial column (Smiley Anders' column in The Advocate), notices placed at several local area department and grocery stores, letters describing the study that were sent to members of the local Restless Legs Syndrome Foundation Support Group, and a notice describing the study that was placed on the Psychology experiment sign-up board in Audubon Hall. The RLS patients who were receiving medication for their RLS were required to obtain written approval from their physician to temporarily withdraw from treatment before participating in the research project (for one day/night).

As noted earlier, all six of the PLMS subjects were recruited as normal control subjects; none had been previously diagnosed with PLMS, nor were any of them receiving any medication for any sleep-related problem. The PLMS subjects were recruited from among the older L.S.U. undergraduate psychology students and parents of younger L.S.U. students enrolled in undergraduate

psychology courses. PLMS subjects who were students themselves were given extra credit in their psychology courses for their participation in the study. PLMS subjects who were the parents of students were not directly compensated for their participation. However, their children were given extra credit in their psychology courses for their assistance in recruiting their parents as subjects for the study.

The normal subjects were also recruited from among the older L.S.U. students and parents of students enrolled in undergraduate psychology classes. As with the PLMS group, control subjects who were students themselves were given extra credit in their psychology courses for their participation in the study. Control subjects who were the parents of students were not directly compensated for their participation; instead, their children were given extra credit in their psychology courses for their assistance in recruiting their parents as subjects for the study. Near the end of the data collection period, approval was obtained from the Institutional Review Board to recruit control subjects with notices placed at local department and grocery stores, and to compensate these subjects with a $25.00 payment for their participation. Two control subjects were recruited in this manner.

Cancellations, no-shows, and last-minute rescheduling were a problem during the data collection period, and contributed to the low sample sizes achieved. In all, there were eleven instances of cancellations, no-shows, or last-minute rescheduling; almost all of these involved weekend nights.

Apparatus

The SIT and polysomnograms were conducted in the L.S.U. Department of Psychology's Psychophysiological Laboratory, which contained a ten by eleven foot sound-attenuated subject room, and a similarly sized instrument room. The subject room was furnished with a full-size bed (measuring approximately 54 by 75 inches), a recliner, a nightstand, a television and VCR, and two cabinets containing supplies. The room was also equipped an infrared lamp (mounted above the door), and a JVC model TK-S240V video camera. These were used to monitor the subject visually during the recordings. The camera was connected to a Toshiba TVM-1202 12 inch black and white monitor which was located in the instrument room.

The cerebral oximeter used in the study was the Somanetics (Troy, Michigan) INVOS 3100A cerebral oximeter with software version V5.13X5. This device consisted of a small sensor (3.5 by 1.75 inches) that connected to a small (7.5 by 5.3 by 1.75 inch) preamplifier via a five

foot cable. The Somanetics corporation loaned us two of these instruments for use in the study. The preamplifiers were located in the subject room, and were connected to the oximeters via the supplied fifteen foot cable. The oximeters were located in the instrument room, and were relatively small in size (13.6 by 12.3 by 6.4 inches). Analog output (a zero to ten volt signal of the rSO_2 index) from the oximeter was sent to the J5 input of a Grass Instruments Model 7P122 low level DC amplifier with the signal amplitude reduced down to a maximum of one volt with a locally constructed voltage divider (instructions for making the voltage divider were provided by the Somanetics corporation). The digital output from the oximeter was sent to a Dell Optiplex GXi Pentium processor-based personal computer via a null modem cable. The Hyperterminal program included with Windows 95 was used to display and store the data on the computer. The data were retrieved for subsequent analysis by loading them into a spreadsheet program (Microsoft Excel).

Leg movement activity from both legs, abnormal leg sensations, one channel of EEG (C4/A1), nasal airflow, respiratory effort, and peripheral pulse oximetry were recorded during the SIT on a Grass Instruments (Quincy, Massachusetts) Model 7D polygraph. Specifically, anterior

tibialis EMG was recorded from both legs using Grass Instruments 10 mm gold cup electrodes, and standard electrode site placements (ASDA Atlas Task Force, 1993). Each of the tibialis EMG signals was sent to a Grass Instruments Model 7P511 EEG amplifier, with the sensitivity set so that a slow 30 degree dorsiflexion and plantarflexion of the great toe produced an EMG burst that was 75% of the amplitude of the full scale deflection range of the pen. Leg sensations were recorded by having the subjects depress a signal marker that was connected to the power supply of the Grass polygraph via an eight foot cable. This signal was displayed on the time line of the chart recorder. EEG (C4/A1) was recorded with Grass Instruments 10 mm gold cup electrodes, with the signal sent to a Grass Instruments Model 7P511 EEG amplifier with the sensitivity set at 5 uV/mm. Nasal airflow was recorded with Rochester Electro-Medical "no casing" wire-type thermocouple which was taped beneath the nose. Respiratory effort was recorded with an EPM Systems (Midlothian, Virginia) "Resp-EZ respiratory belt. Both the airflow and respiratory effort signals were sent to Grass Instruments Model 7P511 EEG amplifiers, with the sensitivity settings varied to keep the waveform between 50 and 75% of the full scale deflection of the

oscillograph pen. Peripheral pulse oximetry was recorded with a Criticare Systems (Waukesha, WI) Model 504 PONI oximeter. The "clothespin-type" sensor supplied with the oximeter was attached to either the index or middle finger of the left hand. The analog output signal from the oximeter was sent to a Grass Instruments Model 7P122 low-level DC amplifier.

The polysomnograms were recorded on a Bio-Logic Systems Sleepscan computerized polysomnograph. The EEG, EOG, submental EMG, electrocardiogram, and tibialis EMG signals were transduced with Grass Instruments 10 mm gold cup electrodes. The airflow signal was recorded with an oral/nasal thermocouple manufactured by Pro-Tech Services (Woodinville, Washington). Respiratory effort was recorded with an EPM Systems "Resp-EZ" respiratory belt.

Procedure

All subjects were initially screened by phone to determine if they were likely to meet criteria for inclusion into the study. If they did, they were sent a packet of questionnaires containing two copies of the consent form (see Appendix 2), the Sleep Disorders Inventory, the Daily Sleep Dairy, and Daily Sleepiness Scales (RLS patients also received the Restless Legs Questionnaire). These packets took two weeks to complete. After they were returned, all questionnaires were

reviewed, and a final decision was made to either include or exclude each potential subject in/from the study.

Subjects selected for inclusion into the study were required to report to Audubon Hall at L.S.U. approximately three hours prior to their normal bedtime. In order to run the SIT as close as possible to a subject's normal bedtime, all electrodes and recording devices were attached prior to conducting the SIT.

The EEG electrode sites conformed to the international "Ten/Twenty" system specified by Jasper (1958), and included electrodes at the following sites on the scalp and mastoids: Oz, A1, A2, C3, and C4. One channel of EEG (C4/A1) was recorded on the Grass polygraph, while two channels (C3/A2, Oz/C3) were recorded on the Sleepscan. The C4/A1 and C3/A2 derivations are the standard bipolar derivations recommended by Rechtschaffen and Kales (1968) for recording sleep. The occipital derivation (Oz/C3) was included so that alpha activity could be optimally visualized. Submental EMG was recorded by placing gold cup electrodes on the chin and over the masseter muscle. Electrooculogram was recorded by placing gold cup electrodes at sites that were one centimeter away from the outer canthus of each eye, with both electrodes referred to the A1 electrode. The oral/nasal thermocouple

was taped just under the nares with a hypoallergenic cloth tape (Dermicel, Johnson & Johnson). The electrocardiogram was recorded by placing one gold cup electrode near each shoulder just under the clavicle, thus approximating the Lead 1 ECG lead. Respiratory effort was recorded by placing the respiratory belts over the bedclothes just below the ribcage (approximately three inches above the naval). Regional cerebral hemoglobin oxygen saturation was recorded by placing the Somanetics self-adhesive sensor on the forehead just lateral to the midline. The left side of the forehead was used for all but four subjects. The right side was used for two RLS subjects who reported having worse symptoms in their left legs, and for two of the controls (to control for any possible hemispheric differences in blood flow and hemoglobin oxygen saturation). In three bald subjects (two controls and one PLMS subject) two recording sites were used for measuring cerebral oximetry: the forehead and the vertex of the head. For the vertex recording sites, the sensor was placed on the same side as the forehead sensor, with the long edge of the sensor at the midline, and the midpoint of the sensor at the Cz site. The light emitter end of the sensor was placed anteriorly. This site should have placed the sensor over the sensory/motor cortex for

the legs and torso. Anterior tibialis EMG was recorded with gold cup electrodes placed over the anterior tibialis muscle as specified by the ASDA Atlas Task Force (1993). EEG electrodes were attached to the scalp using collodion soaked gauze squares, which were dried with a small air blower. Gold cup electrodes attached to sites other than the scalp were secured with hypoallergenic cloth tape (Dermicel, Johnson & Johnson). All electrode sites in which Grass gold cup electrodes were used (EEG, EOG, submental EMG, ECG, tibialis EMG) were cleaned and slightly abraded with a pumice based soap (Omni-Prep, D.O. Weaver & Co.). The gold cup electrodes were filled with a conductive paste (Ten20, D.O. Weaver & Co.). The recording site for the Somanetics sensor was cleaned with an alcohol/acetone prep pad as per the manufacturer's recommendations. The EEG electrodes were removed in the morning with gauze soaked in an acetone/water solution.

After all electrodes and recording devices were attached (which took approximately one hour and forty-five minutes), the subjects were allowed to move around for several minutes, so that any restlessness that developed during the electrode hookup could be alleviated. The Suggested Immobilization Test (SIT) began with the subject being instructed to lie down quietly in the bed with eyes

open, while attempting to remain completely still. The subjects were further instructed that if they felt as if they had to move, they should move as little as possible and for as short of a period of time as possible. Only one RLS subject actually had to get up out of bed during the SIT. The subjects were also instructed to depress the button on the hand-held event marker whenever they felt an abnormal sensation in their legs. During the SIT, the experimenter continuously monitored the polygraph and cerebral oximeter, and about once every 90 seconds simultaneously marked the time on both instruments by depressing the event marker on each. The time associated with the event mark in the oximetry data (which was displayed on the computer monitor) was subsequently noted on the polygraph chart recording. The SIT lasted for a period of 60 minutes.

Following the SIT, subjects were allowed to use the restroom, and then the lights were turned out for the night. A recording period of at least six hours was required during each PSG. During the recording, the experimenter marked each PLM by depressing the event marker on the oximeter. The oximeter time and Sleepscan epoch were also frequently marked and noted on the chart recording. After the PSG was terminated, the electrodes

and other recording devices were removed, and the patient was asked to fill out a Daily Sleep Diary. They were then thanked for their participation, and allowed to go home.

The polysomnograms were scored manually using sleep stage criteria specified by Rechtschaffen and Kales (1968), arousal scoring criteria specified by the American Sleep Disorders Association (1992), apnea and hypopnea scoring criteria specified by Bliwise, Bliwise, Kraemer, and Dement (1984), and leg movement scoring criteria specified by the ASDA Atlas Task Force (1993). The following summary statistics were derived from the PSG data: total bed time expressed as a percentage of total lights out time, sleep efficiency (i.e. total sleep time expressed as a percentage of total bed time), sleep onset latency (time in minutes from lights out until the first three consecutive minutes of sleep), percent Stage 1 sleep, percent Stage 2 sleep, percent slow wave sleep (Stage 3 plus Stage 4 time expressed as a percentage of total sleep time), percent REM sleep (expressed as a percentage of total sleep time), number of PLMs per hour of sleep, number of apneas plus hypopneas per hour of sleep (the Apnea plus Hypopnea Index, AHI), number of transient and PLM-related arousals per hour of sleep (this arousal index included all arousals not related to

respiratory events), number of sleep stage changes per hour of sleep, and number of Stage 1 periods per hour of sleep.

The SIT recordings were marked in five second epochs according to the time marks noted during the recording, and the time data in the computer data file. Each five second epoch was then scored for movement in each leg and for sensory events. This information was then entered into the spreadsheet data file containing the downloaded oximetry data.

It was originally proposed to hand score individual B-waves (using a locally derived set of criteria) as any wave occurring in a series of at least four waves with a period of between 15 and 120 seconds, and an amplitude of at least ten percent of the mean rSO_2. This initially proved to be far too time-consuming, so spectral analysis (using the "Proc Spectra" procedure in SAS) was used to determine wave periodicities, while hand scoring was used to measure wave amplitudes. Subsequently, B-wave wavelengths were scored by hand for the rSO_2 index in order to calculate the wave-to-wave change in wavelength.

To control for individual variability in the absolute value of the rSO_2 index, the average B-wave amplitudes for each subject were expressed as a percentage of the mean

rSO_2 index for that subject. Wave amplitudes were much lower than the originally proposed ten percent value.

Wave periods were determined from the spectral analysis graphs (called periodograms) which plotted spectral density on the y-axis and wave period on the x-axis. Spectral density is an indicator of relative wave frequency and amplitude. The periodograms typically showed multiple peaks (varying in number from 2 up to 8 or more on occasion) in the 15 to 90 second range. A peak was defined as any point that was 17% or higher than each of the adjacent troughs (17% represents one sixth of the trough amplitude). For each subject, up to two peaks were counted in each of four 20 second ranges: 11 to 30 seconds, 31 to 50 seconds, 51 to 70 seconds, and 71 to 90 seconds. The period axis was divided into these four ranges because there was a clear tendency for the spectral density value to increase as the period increased (most likely due to higher amplitudes in waves with longer wavelengths). The 0 to 10 second range was excluded because 10 seconds represented the minimum wavelength that could be measured with the oximeter's 0.2 Hz sampling rate; thus, the periodograms contained no spectral density values in the 0 to 10 second range. Peaks were counted only if they were at least 17% higher in amplitude than

the third highest peak in the twenty second range (both peaks were counted if no third peak was present). The periods associated with these peaks were estimated to the nearest second directly from the graphs.

For the analyses investigating where PLMs and SIT sensory and motor events occurred in the B-wave cycle, a set of scoring rules were developed (see Appendix 3) to determine if a given rSO_2 point was a trough, an ascending point, a peak, a descending point, or a stable point. For similar analyses with the total hemoglobin data, only four points were scored (trough, ascending, peak, descending), because the data points varied on a much finer scale, and were never stable for more than two observations. This was in contrast to the rSO_2 data which could remain at the same value for much longer periods of time. To assess the reliability of these scoring rules, two scorers independently scored eight rSO_2 files and thirteen total hemoglobin files. The percent agreement between the two scorers was 99% for the rSO_2 files and 92% for the total hemoglobin files.

If any subject had respiratory events during the PSG, then the oximetry data recorded during the event, and one minute prior to and after the event, were excluded from analysis. Similarly, if a normal control subject did have

PLMs during the PSG, the oximetry data throughout the PLM sequence(s) were excluded from the data analyses.

B-wave amplitudes and periods were scored for the entire SIT period for all subjects (no RLS subject had any substantial period during the SIT without any symptoms). For the sleep data in PLMS subjects, B-wave amplitudes and periods were scored during all PLM series that contained at least ten PLMs each. Three of the thirteen subjects who did have PLMS had one such PLM series, seven had two series, two had three series, and one had four series. The rSO_2 data (e.g. wave amplitudes, rSO_2 at PLMs) were averaged across all periods for each subject, with the duration of each series being used to weight the data points for each series. To obtain the rSO_2 data in non-PLMS subjects, single 60-minute sections of sleep were used for three subjects, and two 30-minute sections of sleep were used for eleven subjects. These sections of sleep were specifically selected to exclude awakenings and major arousals associated with sleep position changes, and were also matched to the sleep cycle of the sleep periods selected for the PLMS subjects (e.g. first, second, third, etc 90-minute sleep cycle).

Statistical Analyses

Because of the small sample sizes, and the number of tests needed to analyze all the questions of interest, an

alpha level adjustment procedure (described below) was employed. The hypotheses stated above were divided into two groups which differed in their importance with respect to testing the PCI theory of RLS and PLMS, and with respect to the nature of the dependent variables involved. The most important hypotheses tested were those concerning group differences in the rSO_2 index during the SIT and PSG, the analyses concerning within subjects differences in the rSO_2 index at the beginning of RLS/PLMS symptoms compared to the rSO_2 index occurring at the B-wave peaks, and the analyses concerning within subjects differences in the percentage of RLS sensory/motor events and PLMs occurring at different points in the B-wave cycle. The hypotheses of secondary importance were those concerning group differences in the SIT and PSG variables. Differences in these variables were expected to occur (based on the procedures used to define the groups), but were not directly relevant to tests of the PCI theory of the pathogenesis of RLS and PLMS.

In order to use alpha levels that reflected the differing importance of the experimental hypotheses, the statistical tests of the rSO_2 data employed an alpha level based on the total number of tests used to analyze the

rSO_2 data (20), while the statistical tests of the SIT and PSG data employed an alpha level based on the total number of statistical tests used in the entire study (53). This use of different alpha levels to test hypotheses of differing importance is recommended by Tabachnick and Fidell (1989, pp. 49-50).

In addition to this, a multistage Bonferroni procedure for adjusting alpha levels described by Larzelere and Mulaik (1977) was used. Although this procedure was developed for use in correlational analyses, Huberty and Morris (1989) recommended it for studies in which multiple ANOVAs were to be used. The procedure is based on Monte Carlo studies, briefly described in Larzelere and Mulaik (1977), which showed that the Bonferroni procedure is unnecessarily conservative when a large percentage of the hypotheses tested involve null hypotheses that are actually false. This multistage Bonferroni correction procedure is conducted as follows. In the first stage, the traditional Bonferroni procedure of dividing the alpha level (.05) by the number of tests (20 and 53 in the proposed study) is used to determine the initial alpha level. If none of the statistical tests reaches significance at this level, then one stops (with none of the null hypotheses having been rejected). If one

or more tests do reach significance at this level, then one moves to the second stage. In the second stage, a new corrected alpha level is determined by dividing the traditional .05 alpha level by the number of tests in the first stage in which the null hypothesis was not rejected. The results of the statistical tests are then re-examined using this new alpha level. As before, one stops if none of the tests are significant, or moves to another stage if at least one of the null hypotheses is rejected. The procedure ends when one reaches the point at which none of the remaining null hypotheses are rejected.

To employ this procedure in the proposed study, the twenty tests involving the rSO_2 data were initially examined using an alpha level of .0025, while the tests involving the SIT and PSG variables were examined using an alpha level of .001.

The tests of the rSO_2 B-wave amplitude during the SIT and PSG involved a total of six pairwise comparisons of interest. These included all three possible pairwise comparisons of the rSO_2 B-wave amplitude during the SIT, and all three possible pairwise comparisons of the rSO_2 B-wave amplitude during the PSG. These six tests were analyzed with planned F-tests, using weights of 1 and -1 for the two group means. For the directional hypotheses,

the p level attained was divided by two, since the statistical package that was used only gives a p value for a two-tailed hypothesis.

The analyses involving the rSO_2 value at the beginning of SIT sensory/motor events and the beginning of PLMs during sleep involved a total of five tests. These included all three pairwise comparisons for SIT motor events (both RLS and PLMS subjects had motor events, they were compared to each other and to the control mean), RLS versus controls for SIT sensory events (the PLMS and control subjects did not have sensory events), and all patients with PLMs versus controls for the sleep data.

It was originally proposed to compare the average rSO_2 values occurring at the beginning of these events in patients (SIT sensory and motor events, and PLMs in sleep) to the average B-wave trough rSO_2 values in the normal subjects. This was proposed because it was predicted that events in the patients would occur at the B-wave troughs. This prediction was not confirmed; therefore, in lieu of those comparisons, non-directional tests were performed comparing the average rSO_2 values at the event onsets in the patients to the mean values for the controls (the small number of SIT epochs with movement in the control

subjects were not used in computing their average rSO_2 values).

There were six additional tests proposed involving within subjects analyses. These tests included the following: (1) in RLS subjects, the average rSO_2 at SIT sensory and motor events were to be compared to the average rSO_2 value at the next B-wave peak (two tests); (2) in all patients with PLMs (both RLS and PLMS subjects), the average rSO_2 at PLMs were to be compared to the average rSO_2 value at the next B-wave peak (one test); (3) the percentage of SIT sensory and motor events in RLS subjects occurring at each point in the rSO_2 B-wave cycle were to be compared using a within subjects ANOVA (a Chi Square goodness of fit test was used instead; two tests); and (4) in all patients with PLMs the percentage of PLMs occurring at each point in the B-wave cycle were also to be compared using a within subjects ANOVA (again, a Chi Square goodness of fit test was used; one test). Because the last three tests were so important for testing the PCI theory, it was decided to conduct three similar tests with the total hemoglobin data. These additional tests increased the total number of tests to twenty for the oximetry data. As noted above, the prediction that PLMs and SIT sensory/motor events would occur at B-wave troughs

was not confirmed. Therefore, in lieu of those analyses (the first three discussed above), non-directional paired-sample t-tests were performed comparing the rSO_2 values at the onset of PLMs and SIT sensory/motor events to the average rSO_2 values where no abnormal sensations, movement, or PLMs were present.

Table 1 summarizes the 20 tests involving the oximetry data, and the predictions made for each of them. The last two tests listed in the table actually represent a total of six tests (SIT sensory and motor events in both the rSO_2 and total hemoglobin B-wave cycles (for the RLS subjects), and PLMs in both B-wave cycles (for the PLMS subjects).

The SIT and PSG data involved a total of 33 pairwise comparisons, all of which were tested with planned F-tests. These 33 tests and the predictions associated with them are summarized in Table 2. All of the hypotheses for tests involving comparisons between the RLS and normal control groups were directional, while six of the eleven comparisons between the PLMS group and the normal group, and five of the eleven comparisons between the RLS and PLMS group, were directional. Two of the comparisons between the PLMS and normal controls (those for the SIT sensory index and total bed time variables) involved

Table 1. Summary of Statistical Tests of rSO_2 Data

Comparison	Variable(s)	Prediction
RLS & Normals	SIT B-wave amplitude	RLS > Normals
PLMS & Normals	SIT B-wave amplitude	none
RLS & PLMS	SIT B-wave amplitude	RLS > PLMS
RLS & Normals	PSG B-wave amplitude	RLS > Normals
PLMS & Normals	PSG B-wave amplitude	PLMS > Normals
RLS & PLMS	PSG B-wave amplitude	RLS = PLMS
RLS & Normals	SIT sensory/mean rSO_2	RLS = Normals
RLS & Normals	SIT motor/mean rSO_2	RLS = Normals
PLMS & Normals	SIT motor/mean rSO_2	PLMS = Normals
RLS & PLMS	SIT motor event rSO_2	RLS = PLMS
PLMS & Normals	PLM/mean rSO_2	PLMS = Normals
RLS (Within Ss)	SIT sensory rSO_2	event=no event
RLS (Within Ss)	SIT motor rSO_2	event=no event
PLMS (Within Ss)	PLM and no-event rSO_2	PLM = no PLM
RLS (Within Ss)	% of events at various points in B-wave cycle	significant
PLMS (Within Ss)	% of PLMs at various points in B-wave cycle	significant

predictions that there would be no group differences, while no prediction was made for the PLMS/normal group comparisons on three other dependent variables.

Table 2. Summary of Statistical Tests of SIT and PSG Data

Variable	RLS/Normals	PLMS/Normals	RLS/PLMS
SIT Sensory	RLS > Normals	PLMS = Normals	RLS > PLMS
SIT Motor	RLS > Normals	none	RLS > PLMS
PLM Index	RLS > Normals	PLMS > Normals	none
Bed Time	RLS < Normals	PLMS = Normals	RLS < PLMS
Efficiency	RLS < Normals	none	RLS < PLMS
Latency	RLS > Normals	none	RLS > PLMS
Light Sleep	RLS > Normals	PLMS > Normals	none
Percent SWS	RLS < Normals	PLMS < Normals	none
Arousals	RLS > Normals	PLMS > Normals	none
Stage Changes	RLS > Normals	PLMS > Normals	none
Stg 1 Periods	RLS > Normals	PLMS > Normals	none

Similarly, no prediction was made for the RLS/PLMS comparisons on six dependent variables because it was unclear from the RLS/PLMS literature whether or not such differences should be expected. The eleven tests in which either no prediction was made or in which no group differences were predicted were tested with two-tailed tests.

Finally, one of the experimental hypotheses (number 2) was descriptive in nature, and did not require the use

of an inferential statistical test. This was the prediction that waking sensory events in RLS subjects would be brief and periodic.

Results

SIT and PSG Data

The group means and standard deviations for the SIT sensory and motor indices and the nine sleep variables are listed in Table 3. An examination of the standard deviations shows that the RLS group had relatively high

Table 3. Group means for SIT and PSG data.

Variable[1]	RLS	PLMS	Controls
SIT SI	50.3 (60.4)	0 (-)	0.1 (0.3)
SIT MI	86.4 (40.7)	16.5 (12.8)	5.3 (5.7)
PLMi	35.0 (33.5)	22.5 (14.3)	2.3 (2.5)
%TIB	93.3 (15.3)	99.2 (1.2)	98.7 (1.3)
Latency	89.6 (124.2)	19.2 (13.1)	21.5 (20.5)
Efficiency	67.0 (19.9)	84.4 (13.4)	81.6 (9.8)
Stage 1 %	12.4 (5.7)	9.6 (5.4)	14.5 (7.2)
SWS %	12.4 (13.6)	13.9 (9.0)	14.7 (7.2)
Arousals	13.5 (4.6)	10.2 (4.4)	13.3 (3.9)
Stg Changes	24.7 (7.2)	23.5 (3.9)	25.6 (7.2)
S1 Periods	6.2 (2.2)	5.6 (2.9)	7.6 (2.9)

1) Abbreviations are as follows: SIT SI = SIT sensory index, SIT MI = SIT Motor index, PLMi = Periodic Limb Movement Index, %TIB = Percent time in bed, Arousals = Arousals per hour of sleep, Stg Changes = stage changes per hour of sleep, S1 Periods = Stage 1 Periods per hour of sleep.

relatively high standard deviations (relative to their group mean) on the first six variables in Table 3. Similarly, the control group had high standard deviations relative to their means on the four of the first six variables (SIT SI, SIT MI, PLMi, and Latency). The SIT sensory index was noteworthy in that no PLMS subject had any abnormal sensations during the SIT, while only one control subject had a single abnormal sensation. Levene tests for homogeneity of variance on all eleven variables in Table 3 were significant for the first six (SIT SI, SIT MI, PLMi, %TIB, Latency, and Efficiency). Shapiro-Wilk tests for normality on all eleven variables for all three groups showed that only two variables (Arousals and Stage Changes) were normally distributed for all three groups. Because of these departures from normality and homogeneity of variance, non-parametric Mann-Whitney U tests were used in lieu of the planned F-tests for all variables except Arousals and Stage Changes. The Mann-Whitney test is a rank procedure which yields a z-ratio with a p-level corrected for ties.

Table 4 shows the z and t values (and the p values associated with them), for the pairwise comparisons on the eleven SIT and PSG variables. Using the corrected alpha level of .001, three of the comparisons in Table 4

Table 4. Statistical Results for SIT and PSG Data

Variable	RLS/Controls	RLS/PLMS	PLMS/Controls
SIT SI	-3.22 (.0007)	-2.68 (.0037)	-0.73 (n.s.)
SIT MI	-3.68 (.0001)	-2.95 (.0016)	-2.07 (.04)
PLMi	-2.79 (.0026)	-0.24 (n.s.)	-3.34 (.0004)
%TIB	-0.16 (n.s.)	-0.66 (n.s.)	-0.76 (n.s.)
Latency	-1.52 (n.s.)	-1.18 (n.s.)	-0.20 (n.s.)
Efficiency	-1.71 (.04)	-2.36 (.009)	-0.70 (n.s.)
Stage 1 %	-0.30 (n.s.)	-0.83 (n.s.)	-1.71 (n.s.)
SWS %	-1.48 (n.s.)	-0.94 (n.s.)	-0.20 (n.s.)
Arousals	-0.13 (n.s.)	1.43 (n.s.)	-1.49 (n.s.)
Stg Changes	0.32 (n.s.)	0.62 (n.s.)	-0.33 (n.s.)
S1 Periods	-1.07 (n.s.)	-0.94 (n.s.)	-1.61 (n.s.)

would be considered significant: the SIT SI between the RLS and controls, the SIT MI between the RLS and controls, and the PLMi between the PLMS and controls. Four other comparisons reached low p values, and would probably have been significant if the sample sizes had been larger: the SIT SI between the RLS and PLMS subjects, the SIT MI between the RLS and PLMS subjects, the PLMi between the RLS and control subjects, and sleep efficiency between the RLS and PLMS subjects. It is also worth pointing out that

if the corrected alpha level had been set at .0038 (which would have held the experiment-wise Type 1 error rate at 0.2), then the SIT SI and MI comparisons between the RLS and PLMS groups, and the PLMi comparison between the RLS and control group would have been significant.

SIT Sensory Events in RLS Subjects

Individual subject data for the SIT sensory events is presented in Table 5. Two of the nine RLS subjects did not report any abnormal sensations, although one of these did report a very low level nearly continuous awareness of her usual sensory discomfort that she could not precisely identify as being present at one moment and not the next. Table 5 also lists the mean sensory event duration and inter-event-interval (IEI) in seconds, and the percent of events which occurred in a series of at least four events with IEIs of greater than 5 but less than 90 seconds. Only three subjects (012, 020, 026) had a majority of events that met the PLMS criteria of four events in a series with IEIs of between 5 and 90 seconds; however, when considering the full PLMS criteria (including event duration of less than 5 seconds), only subjects 020 and 026 had a majority of their sensory events conform to the full PLMS criteria. If the IEI criteria were changed to greater than 20 but less than 90 seconds, then neither of

Table 5. SIT Sensory Events in RLS Subjects

Subj[1]	# of Events	Mean Duration	Mean IEI	% in series of 4 with IEI >5, <90s
012	52	9.5	59.9	71%
017	24	1.1	145.0	0%
020	156	3.9	15.3	78%
034	22	0.5	163.5	0%
026	165	5.0	11.7	59%
030	9	1.2	375.6	0%
057	41	1.2	83.2	0%

1) Abbreviations: Subj = subject, IEI = inter-event-interval.

these subjects would have had more than seven percent of their events conform to the PLMS criteria. Three of the subjects had sensory events of relatively long duration (012, 020, and 026). Not surprisingly, subjects with fewer events had longer IEIs. In general, the sensory events observed in these RLS patients did not appear similar to PLMS in their temporal characteristics. A good description of RLS sensory events based on the present data would be that their temporal characteristics are highly variable between subjects.

The movement data in the RLS subjects also deserve brief comment. The average MI for both legs ranged from 21 to 150, with the group mean being 86. Movement was much more prominent than abnormal sensations. For example, when considering group means, abnormal sensations were present for 18% of the five second SIT epochs, while movement was present for 44% of the five second SIT epochs. Only three subjects had any clear periodicity to their movements, including one who appeared to be having waking PLMs. A more common finding, particularly near the end of the SIT was that the movements were often of long duration (i.e. greater than 30 seconds) and were sometimes nearly continuous. Similar movement was observed prior to sleep onset in several subjects during the PSG recording. In addition, when symptoms were severe, the leg movements observed were quite agitated in nature, and included vigorous shaking and even stamping of the legs. Thus, abnormal movement was a more prominent feature in these RLS patients than were abnormal sensations.

Oximetry Data

Group means and standard deviations for the SIT rSO_2 B-wave amplitudes were as follows; RLS: 3.1 $\pm$ 0.9 percent, PLMS: 2.5 $\pm$ 0.7 percent, and Controls: 2.6 $\pm$ 0.5 percent. These values are the group means of the average wave amplitude for each subject expressed as a

percentage of that subject's mean rSO_2 level during the SIT. None of the three pairwise comparisons for this variable reached statistical significance at the .0025 level (t values: RLS/Controls, -1.72, p = .05; RLS/PLMS, -1.64, p = .06; PLMS/Controls, 0.15, p = .88). As noted earlier, these amplitudes were substantially lower than expected.

Group means and standard deviations for the PSG rSO_2 B-wave amplitudes were as follows; RLS: 2.6 $\pm$ 0.9 percent, PLMS: 2.3 $\pm$ 0.8 percent, Controls: 2.2 $\pm$ 0.3 percent. None of the three pairwise comparisons for this variable reached statistical significance at the 0.0025 level (t values: RLS/Controls, -1.08, p = .15; RLS/PLMS, -0.89, p = .39; PLMS/Controls, -0.06, p = .48).

The mean and standard deviation for the (actual) rSO_2 value at sensory event onset in the RLS subjects was 64.0 $\pm$ 6.5. This was compared to the average rSO_2 value (where no movement or sensory events were present) during the entire SIT for the control subjects (60.2 $\pm$ 9.5) using a non-directional t-test. This test did not reach statistical significance (t = -1.02, p = .32).

The means and standard deviations for the rSO_2 value at motor event onset was 63.3 $\pm$ 6.0 for the RLS subjects, and 65.0 $\pm$ 3.9 for the PLMS subjects (recall that the PLMS

subjects had an average SIT MI of 16.5 movements). These values were compared to the control subject mean "no-event" rSO_2 (60.2 ± 9.5) using non-directional t-tests. None of the three pairwise comparisons reached statistical significance (t values: RLS/Controls, t = -0.93, p = .36; RLS/PLMS, t = 0.43, p = .67; PLMS/Controls, t = -1.27, p = .22).

The mean and standard deviation for the rSO_2 level at PLM onset in the thirteen subjects who had PLMs was 65.9 ± 4.1. This was compared to the average sleep rSO_2 value for the controls (61.5 ± 7.1) using a non-directional t-test. The result of this test did not reach statistical significance (t = -1.89, p = .07).

For the RLS group, the mean rSO_2 value at sensory event onset (for the seven subjects who had sensory events) was 64.0 ± 6.5. This was compared to the mean rSO_2 value for these seven subjects when no sensory or motor events were present (63.6 ± 6.7) using a non-directional paired-samples t-test. This test was not statistically significant (t = 2.12, p = .08).

For the RLS group, the mean rSO_2 value at motor event onset was 63.3 ± 6.0 (all nine RLS subjects had motor events). This was compared to the average rSO_2 value when no sensory or motor events were present (63.0 ± 6.1, for

all nine subjects) using a non-directional paired-samples t-test. This test was not statistically significant ($t = 1.41$, $p = .20$).

For all subjects with PLMs, the mean rSO_2 value at PLM onset was 65.9 $\pm$ 4.1. This was compared to the average rSO_2 value when no PLMs were present (65.6 $\pm$ 4.1) using a non-directional paired-samples t-test. This test was not statistically significant ($t = 1.76$, $p = .10$).

Event Occurrence in the B-Wave Cycle

The percentage of SIT sensory events occurring at each point in the rSO_2 B-wave cycle (trough, ascending limb, peak, descending limb, stable) for the seven RLS subjects who had sensory events is listed in Table 6. The mean percentages and standard deviations for the group are also listed. A Chi Square goodness of fit test on the group means (entered as frequencies) was performed to determine if the percentages were significantly different from equal percentages in each category (which would have been expected by chance). The Chi Square statistic was 56.40, a value which was significant beyond the 0.0001 p level. Only two subjects (030 and 057) had more than 50 percent of their events at any one point in the wave cycle, both at the rSO_2 peaks.

The percentage of SIT sensory events in RLS subjects occurring at each point in the total hemoglobin B-wave

Table 6. Percent of SIT Sensory Events in RLS Subjects Occurring at Various Points in the rSO_2 B-wave Cycle.

Subj[1]	#	Trough	Ascend	Peak	Descend	Stable
012	51	29.4	5.9	47.1	7.8	9.8
017	23	13.0	0	39.1	13.0	34.8
020	106	23.6	18.9	38.7	17.0	1.9
034	10	30.0	20.0	30.0	20.0	0
026	120	25.0	4.2	42.5	5.8	22.5
030	9	11.1	0	66.7	0	22.2
057	25	4.0	0	76.0	16.0	4.0
Mean		19.4	7.0	48.6	11.4	13.6
S.D.		10.1	8.8	16.6	7.1	13.1

1) Abbreviations are as follows: Subj = Subject, # = Number of events, Ascend = Ascending, Descend = Descending, S.D. = Standard deviation

cycle is listed in Table 7. A Chi Square goodness of fit test on the means yielded a value of 32.80, which was significant beyond the 0.0001 p level. Again, only two subjects (017 and 030) had more than 50 percent of their of their events at any one point in the hemoglobin wave cycle; one at the peaks (017), and one at the troughs (030).

Table 7. Percent of SIT Sensory Events in RLS Subjects Occurring at Various Points in the Total Hemoglobin B-wave cycle.

Subj[1]	# Events	Trough	Ascend	Peak	Descend
012	51	37.3	5.9	39.2	17.6
017	23	21.7	4.3	60.9	13.0
020	106	47.2	9.4	24.5	18.9
034	10	20.0	20.0	40.0	20.0
026	120	41.7	5.8	45.0	7.5
030	9	55.6	0	44.4	0
057	25	28.0	8.0	40.0	24.0
Mean		35.9	7.6	42.0	14.4
S.D.		13.3	6.2	10.8	8.3

1) Abbreviations are as follows: Subj = Subject, # = Number of events, Ascend = Ascending, Descend = Descending, S.D. = Standard deviation

The percentages of SIT motor events in the RLS subjects occurring at each point in the rSO_2 B-wave cycle for the nine RLS subjects are presented in Table 8. Only movements occurring in the leg contralateral to the oximetry sensor were used in this analysis. A Chi Square goodness of fit test on the group means yielded a value of 37.70, which was significant beyond the 0.0001 p level. Only two subjects (034 and 057) had more than fifty

Table 8. Percent of SIT Motor Events in RLS Subjects Occurring at Various Points in the rSO_2 B-wave Cycle.

Subj[1]	#	Trough	Ascend	Peak	Descend	Stable
012	92	34.8	3.3	42.4	9.8	9.8
017	80	28.8	7.5	32.5	3.8	27.5
020	121	28.9	11.6	36.4	21.5	1.7
034	54	20.4	5.6	55.6	18.5	0
026	144	23.6	2.1	41.0	8.3	25.0
030	27	48.1	11.1	22.2	7.4	11.1
050	94	30.9	7.4	43.6	12.8	5.3
049	24	37.5	20.8	20.8	12.5	8.3
057	29	20.7	0	55.2	20.7	3.4
Mean		30.4	7.7	38.9	12.8	10.2
S.D.		8.9	6.3	12.4	6.2	9.8

1) Abbreviations are as follows: Subj = Subject, # = Number of events, Ascend = Ascending, Descend = Descending, S.D. = Standard deviation

percent of their motor events at any one point in the rSO_2 B-wave cycle (both at the peaks).

The percentages of SIT motor events in RLS subjects occurring at each point in the total hemoglobin B-wave cycle for the nine RLS subjects are presented in Table 9. A Chi Square goodness of fit test on the group means

Table 9. Percent of SIT Motor Events in RLS Subjects Occurring at Various Points in the Hemoglobin B-wave Cycle.

Subj[1]	# Events	Trough	Ascend	Peak	Descend
012	92	50.0	13.0	21.7	15.2
017	80	33.8	13.8	42.5	10.0
020	121	45.5	12.4	22.3	19.8
034	54	35.2	11.1	44.4	9.3
026	144	41.0	5.6	39.6	13.9
030	27	59.3	11.1	25.9	3.7
050	94	29.8	9.6	47.9	12.8
049	24	29.2	20.8	33.3	16.7
057	29	41.4	3.4	37.9	17.2
Mean		40.6	11.2	35.1	13.2
S.D.		9.9	5.0	9.8	4.9

1) Abbreviations are as follows: Subj = Subject, # = Number of events, Ascend = Ascending, Descend = Descending, S.D. = Standard deviation

yielded a value of 27.84, which was significant beyond the 0.0001 p level. Only two subjects had more than 50 percent of their events at any one point in the hemoglobin wave cycle (012 and 030), both at the troughs.

The percentages of PLMs occurring at each point in the rSO_2 B-wave cycle for the thirteen subjects who had

Table 10. Percent of Periodic Limb Movements in RLS and PLMS Subjects Occurring at Various Points in the rSO_2 B-wave Cycle.

Subj[1]	#	Trough	Ascend	Peak	Descend	Stable
012	33	30.3	3.0	42.4	24.2	0
020	72	6.9	18.1	69.4	2.8	2.8
034	344	16.3	27.0	48.8	7.6	0.3
033	44	9.1	6.8	56.8	20.5	6.8
026	305	13.4	6.9	60.0	7.9	11.8
030	139	24.5	16.5	48.2	3.6	7.2
052	116	28.4	15.5	46.6	8.6	0.9
050	24	37.5	0	25.0	8.3	29.2
049	130	8.5	5.4	61.5	22.3	2.3
056	297	14.8	3.7	56.6	7.4	17.5
060	35	17.1	8.6	51.4	8.6	14.3
066	115	24.3	2.6	39.1	9.6	24.3
069	106	14.2	0	21.7	0	64.2
Mean		18.9	8.8	48.3	10.1	14.0
S.D.		9.4	8.1	13.8	7.5	17.8

1) Abbreviations are as follows: Subj = Subject, # = Number of events, Ascend = Ascending, Descend = Descending, S.D. = Standard deviation

PLMs (this included seven RLS subjects in addition to the six PLMS subjects) are presented in Table 10. A Chi

Square goodness of fit test on the group means yielded a value of 52.10, which was significant beyond the 0.0001 p level. Seven of the thirteen subjects had more than 50 percent of their PLMs at one point in the B-wave cycle; six of these were at peaks, and one was during stable points. For eleven of the thirteen subjects the rSO_2 peak was the wave point with the highest percentage of their PLMs.

The percentages of PLMs occurring at each point in the total hemoglobin B-wave cycle for the thirteen subjects who had PLMs are listed in Table 11. A Chi Square goodness of fit test on the group means yielded a value of 23.76, which was significant beyond the 0.0001 p level. Five subjects had more than 50 percent of their PLMs at one point in the B-wave cycle; at the peaks for three subjects, and at the troughs for two subjects. Seven of the subjects had the greatest percentage of their PLMs at the hemoglobin wave peaks, while six had the greatest percentage of their PLMs at the hemoglobin troughs.

In summary, none of the events studied (SIT sensory events, SIT motor events, and PLMs) occurred at any one point in either the rSO_2 or total hemoglobin B-wave cycle

Table 11. Percent of Periodic Limb Movements in RLS and PLMS Subjects Occurring at Various Points in the Total Hemoglobin B-wave cycle.

Subj[1]	# Events	Trough	Ascend	Peak	Descend
012	33	42.4	3.0	36.4	18.2
020	72	9.7	11.1	75.0	4.2
034	344	59.6	14.5	19.8	6.1
033	44	20.5	15.9	47.7	15.9
026	305	31.8	16.7	44.6	6.9
030	139	15.8	23.7	55.4	5.0
052	116	35.7	15.5	33.0	15.7
050	24	33.3	16.7	37.5	12.5
049	130	36.4	9.3	33.3	20.9
056	297	25.9	6.4	51.5	16.2
060	35	28.6	17.1	31.4	22.9
066	115	48.7	11.3	28.7	11.3
069	106	52.8	4.7	30.2	12.3
Mean		33.9	12.8	40.3	12.9
S.D.		14.5	5.8	14.4	6.1

1) Abbreviations are as follows: Subj = Subject, # = Number of events, Ascend = Ascending, Descend = Descending, S.D. = Standard deviation

more than 50 percent of the time. In five of the six cases however, the events occurred more often at peaks

than at any other point in the cycle. The most consistent findings were that SIT sensory events and PLMs occurred at rSO_2 peaks 49 and 48 percent of the time respectively. All six of the Chi Square goodness of fit tests were highly significant (and well beyond the corrected alpha level of 0.0025 used for the oximetry data).

Figure 1 shows a short segment (6.5 minutes) of rSO_2 raw data during sleep (with the PLMs marked with asterisks) for subject 034. This subject had the largest rSO_2 B-wave amplitude during sleep of any subject with PLMs, and had 49 percent of his PLMs at rSO_2 B-wave peaks. In the segment shown, there are seventeen B-waves, and one PLM per wave. Two of the PLMs occurred at troughs, five during the ascending limbs, and ten at the peaks.

Figure 2 shows a short segment (6.5 minutes) of total hemoglobin raw data during sleep for subject 020 (with PLMs marked with asterisks). This subject had 75 percent of his PLMs at the total hemoglobin B-wave peaks. In the segment shown, there are fourteen B-waves and eleven PLMs, ten of which occurred at peaks, and one which occurred during an ascending limb.

Spectral Analysis Results

The spectral analyses revealed that the oximetry data (both the rSO_2 and total hemoglobin signals) were characterized by multiple wavelengths in the 11 to 90

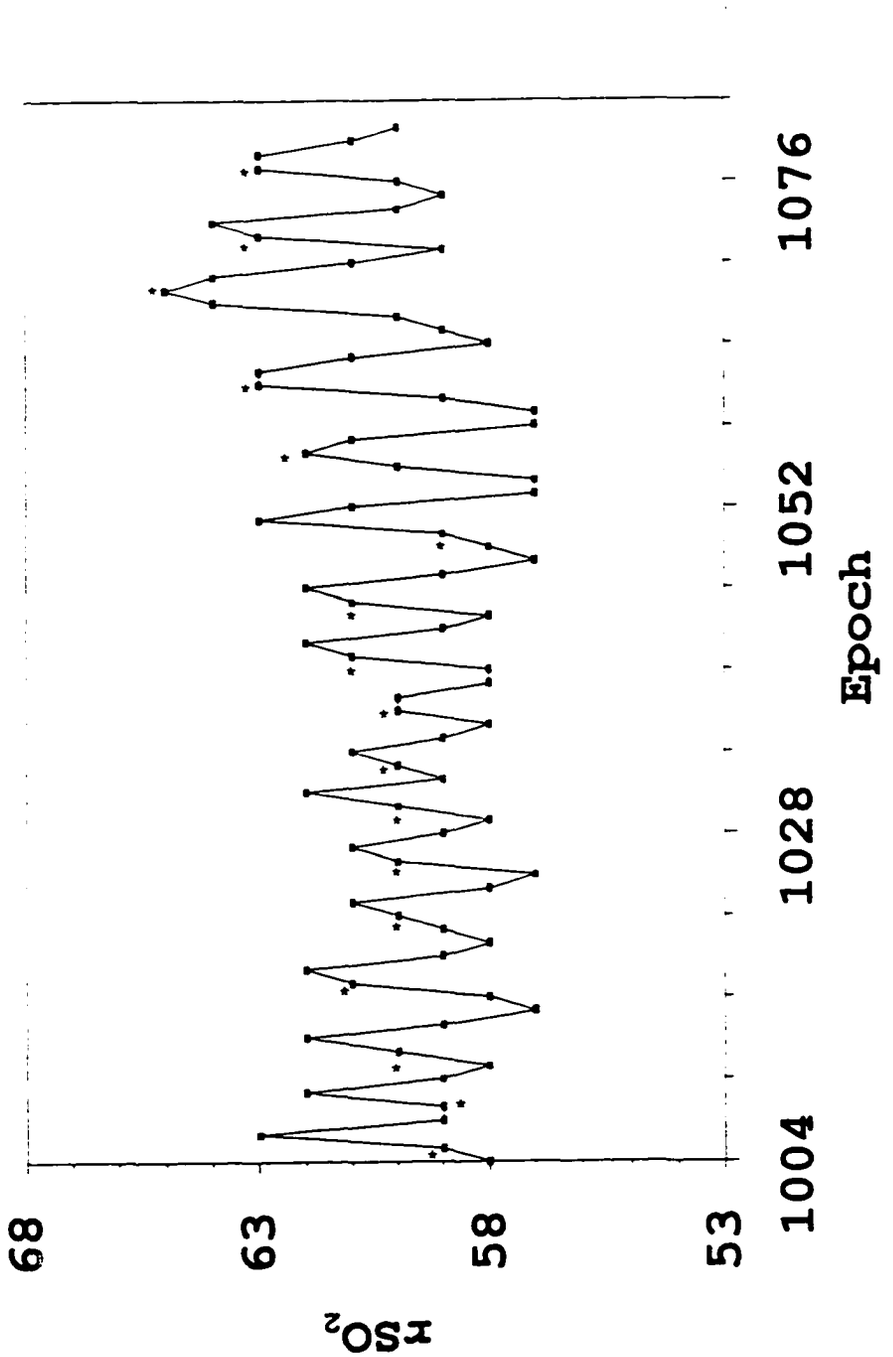

Figure 1. B-waves in rSO_2 in a RLS Subject with PLMs (Note: PLMs are marked with asterisks)

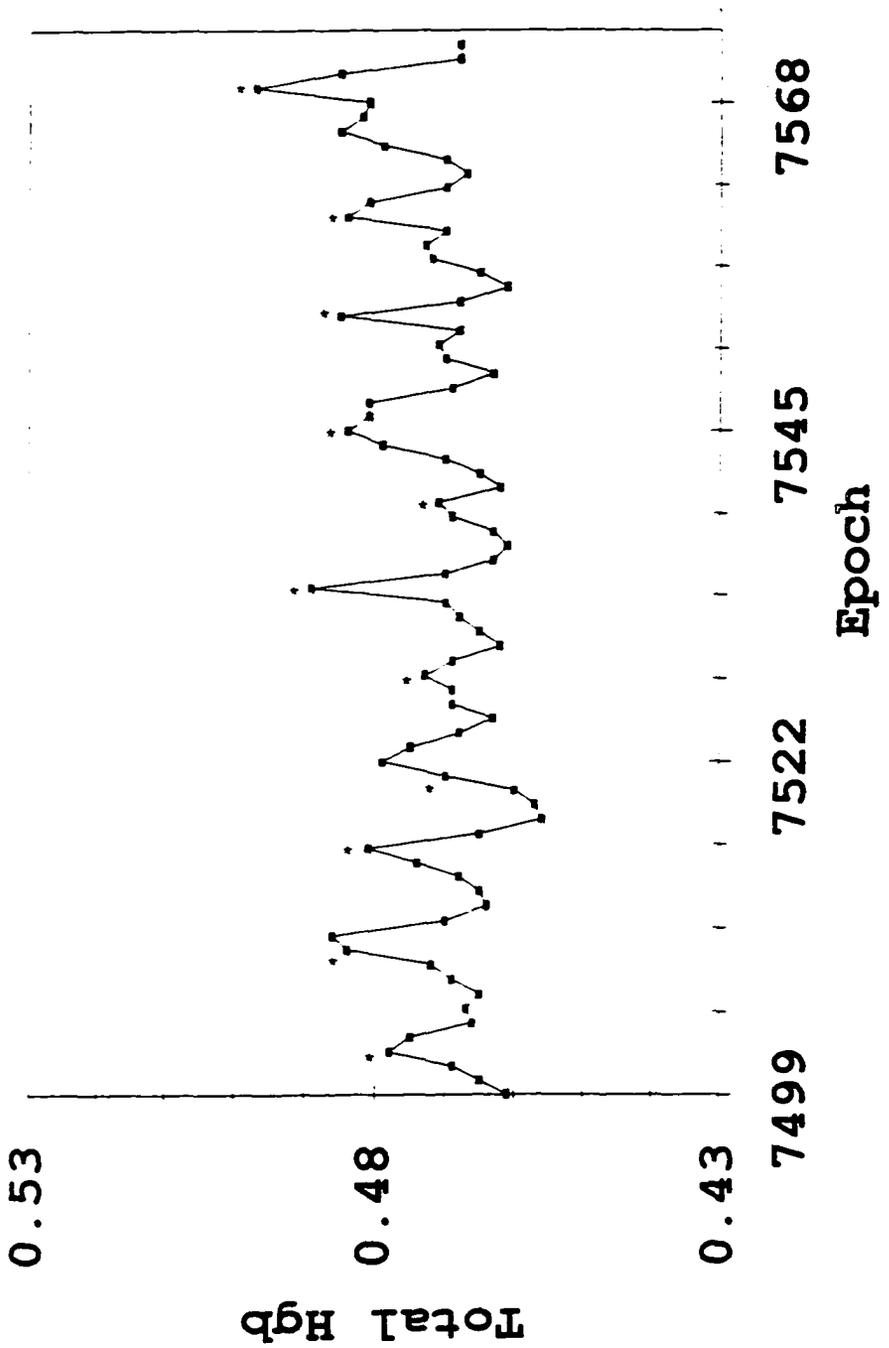

Figure 2. B-waves in Total Hemoglobin in a RLS Subject with PLMs. (Note: PLMs are marked with asterisks)

second range for all groups. Wavelengths were determined from the spectral analysis periodogram graphs by determining the wavelength associated with each periodogram peak. In the following discussion, the word peak refers to a periodogram peak rather than an individual B-wave peak.

For rSO_2 during the SIT, the RLS group had an average of 5.3 peaks per subject, the PLMS group had an average of 5.2 peaks per subject, and the Control group had an average of 4.7 peaks per subject. For total hemoglobin during the SIT, the RLS group had an average of 4.6 waves per subject, the PLMS group had an average of 4.3 waves per subject, and the Control group had an average of 4.2 waves per subject.

The spectral analyses on the sleep data (for controls and subjects with PLMs) were performed with all sleep segments for each subject combined into a single data file. The mean number of rSO_2 peaks was 4.5 ± 1.6 for the PLMS subjects, and 5.2 ± 0.8 for the controls. The mean number of total hemoglobin peaks was 4.5 ± 1.8 for both the PLMS and Control groups.

Table 12 shows the number of periodogram peaks in each group (all peaks for every subject in each group were counted) in each of the eight 10 second ranges from 11 to

90 seconds during the SIT. Data are included for both rSO_2 and total hemoglobin, and are presented to provide descriptive information only (no statistical tests were conducted). For both rSO_2 and total hemoglobin, all three groups had few (if any) peaks in the 11 to 20 second range. For rSO_2 the RLS group had the largest number of peaks in the 31 to 40 second range, and the second largest number of peaks in the 51 to 60 second range. For total hemoglobin the RLS group had the greatest number of peaks in the traditional B-wave wavelength range of 51 to 60 seconds, and the second largest number of peaks in the 31 to 40 second range. The PLMS group had the greatest number of rSO_2 peaks in the 31 to 40 second range, and the second largest number in each of the three ranges from 51 to 80 seconds. For total hemoglobin the PLMS group had the greatest number of peaks in the 51 to 60 second range, and the second largest number of peaks in four ranges (31 to 50 seconds, and 61 to 80 seconds). The control group had the largest number of rSO_2 peaks in the 41 to 50 second range, and the second largest number of peaks in two ranges (51 to 60 seconds and 71 to 80 seconds). The control group had the smallest percentage of rSO_2 peaks of all three groups in the three ranges from 11 to 40 seconds. For total hemoglobin, the control group had the

Table 12. Number of Periodogram Peaks in Each Group in the Different Wavelength Ranges during the Suggested Immobilization Test[1]

Grp	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
				rSO_2 Data				
RLS	1	7	9	7	8	5	4	7
PLMS	0	3	7	3	5	5	5	3
Con	1	5	4	12	9	8	9	4
				Total Hemoglobin Data				
RLS	1	4	7	5	10	6	5	3
PLMS	0	3	4	4	5	4	4	2
Con	0	5	7	7	8	9	5	6

1) Abbreviations are as follows: Grp = group, Con = control. (Wavelength ranges are in seconds).

greatest number of peaks in the 61 to 70 second range, and the second greatest number in the adjacent 51 to 60 second range.

In summary, the spectral analyses showed that subjects in all three groups had multiple rSO_2 and total hemoglobin (wavelength) peaks during the SIT. These included wavelengths in the traditional B-wave wavelength range of 50 to 70 seconds, and wavelengths in most of the

other ranges from 11 to 90 seconds with the exception of the 11 to 20 second range.

Table 13 lists the number of periodogram peaks for the thirteen subjects with PLMs (seven RLS subjects and six PLMS subjects) and for the Control group in each of the eight 10-second wavelength ranges from 11 to 90 seconds for both oximetry variables during sleep. For rSO_2 the PLMS subjects had the greatest number of peaks in the 41 to 50 second range, and the second greatest number of peaks in the 71 to 80 second range. The control subjects had the greatest number of peaks in the 51 to 60 second range, and the second greatest number of peaks in the 31 to 40 second range. For total hemoglobin, the PLMS subjects had the greatest number of peaks in the 21 to 30 second range, and the second greatest number of peaks in the 61 to 70 second range. The control subjects had the greatest number of peaks in the 21 to 30 second range, and the second greatest number of peaks in the 51 to 60 second range.

In summary, the distribution of peaks appeared to be roughly similar for both groups for total hemoglobin, while for rSO_2 the PLMS subjects appeared to have a relatively larger number peaks in the 71 to 90 second range than the control subjects. For both groups there

Table 13. Number of Periodogram Peaks in Control Subjects and Subjects with PLMs in the Different Wavelength Ranges during Sleep[1]

Grp	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
				rSO_2 Data				
PLMS	2	7	9	12	8	4	10	7
Con	1	8	11	7	12	9	6	3
				Total Hemoglobin Data				
PLMS	2	11	7	8	8	10	6	6
Con	1	10	4	8	10	8	7	1

1) Abbreviations are as follows: Grp = Group, PLM = Periodic Limb Movements in Sleep, Con = Control (Wavelength ranges are in seconds).

were very few peaks in the 11 to 20 second range for both variables. As with the SIT data, the spectral analyses showed that during sleep both PLMS and control subjects tended to have a mixture of different wavelengths in their rSO_2 and total hemoglobin data.

Finally, Figure 3 shows a spectral analysis periodogram for a segment of rSO_2 data during sleep in a RLS/PLMS subject. The values on the period axis in this figure represent the number of five-second epochs (e.g. "5" represents a wavelength of 25 seconds). The figure

shows two large peaks at 34 and 58 seconds, and one very small peak at 19 seconds. Figure 4 shows a spectral analysis periodogram for a segment of total hemoglobin data during sleep for a control subject. The periodogram shows two large peaks at 48 and 57 seconds, one medium size peak at 34 seconds, and one small peak at 29 seconds.

Wave-to-Wave Change in Wavelength Data

For the rSO_2 data, individual wave wavelengths were measured for each subject during both the SIT and PSG, and the mean change in wavelength from one wave to the next wave was computed. Lower values for this wave-to-wave change in wavelength number are indicative of more regular and uniform waveforms. Such uniformity has been reported to be characteristic of B-wave activity; thus, this analysis was done in an attempt to determine how many subjects were having relatively unambiguous B-wave activity. A visual examination of the rSO_2 graphs suggested that when the mean wave-to-wave change in wavelength was fifteen seconds or less, there were often sections in the rSO_2 signal that appeared to have the regularity characteristic of B-wave activity. Individual subject data on this variable are presented in Table 14. There were only 14 instances (out of 51) where the mean wave-to-wave change in wavelength was 15 seconds or less, and only three instances where it was 10 seconds or less.

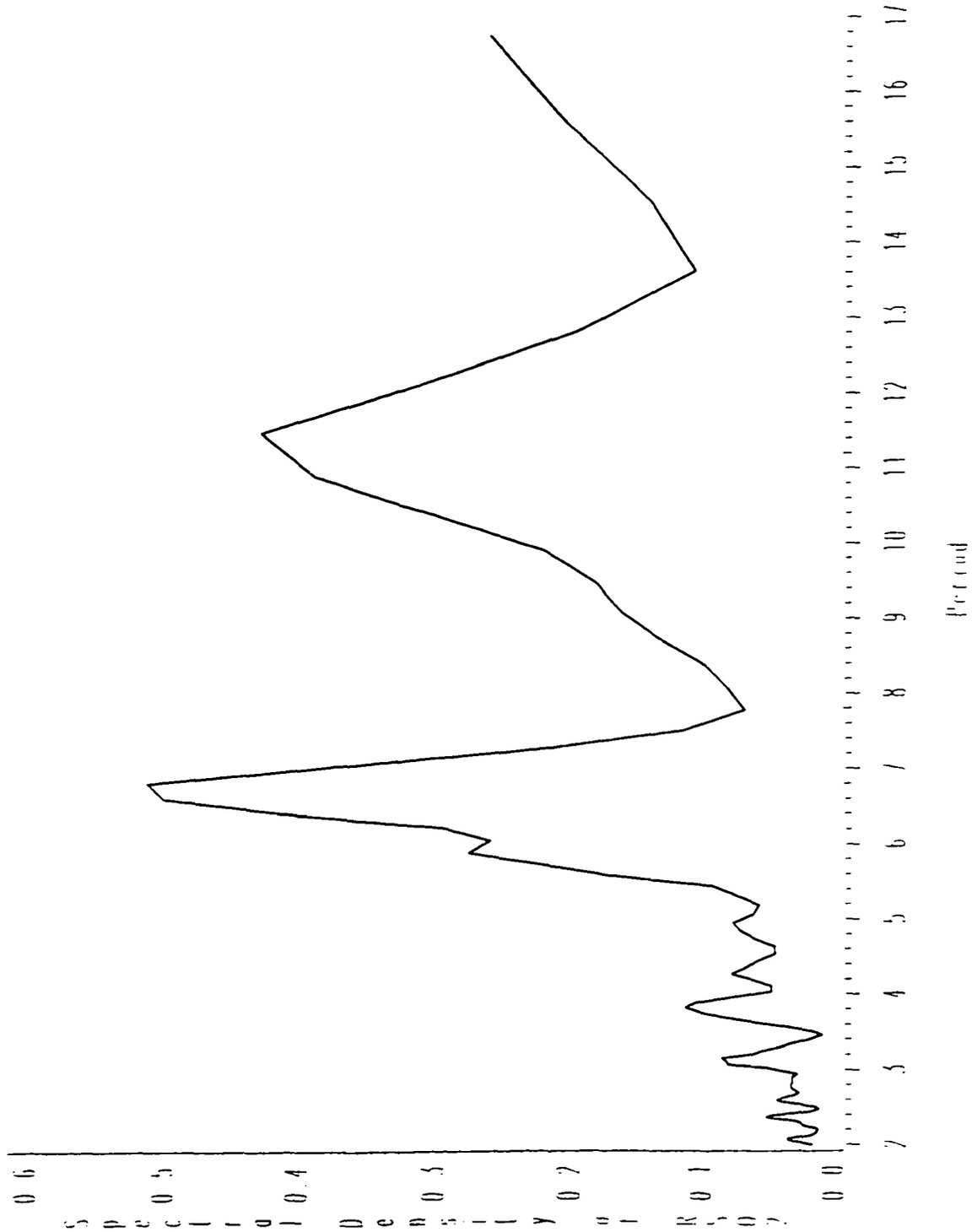

Figure 3. Representative Spectral Analysis Periodogram of rSO_2 Data

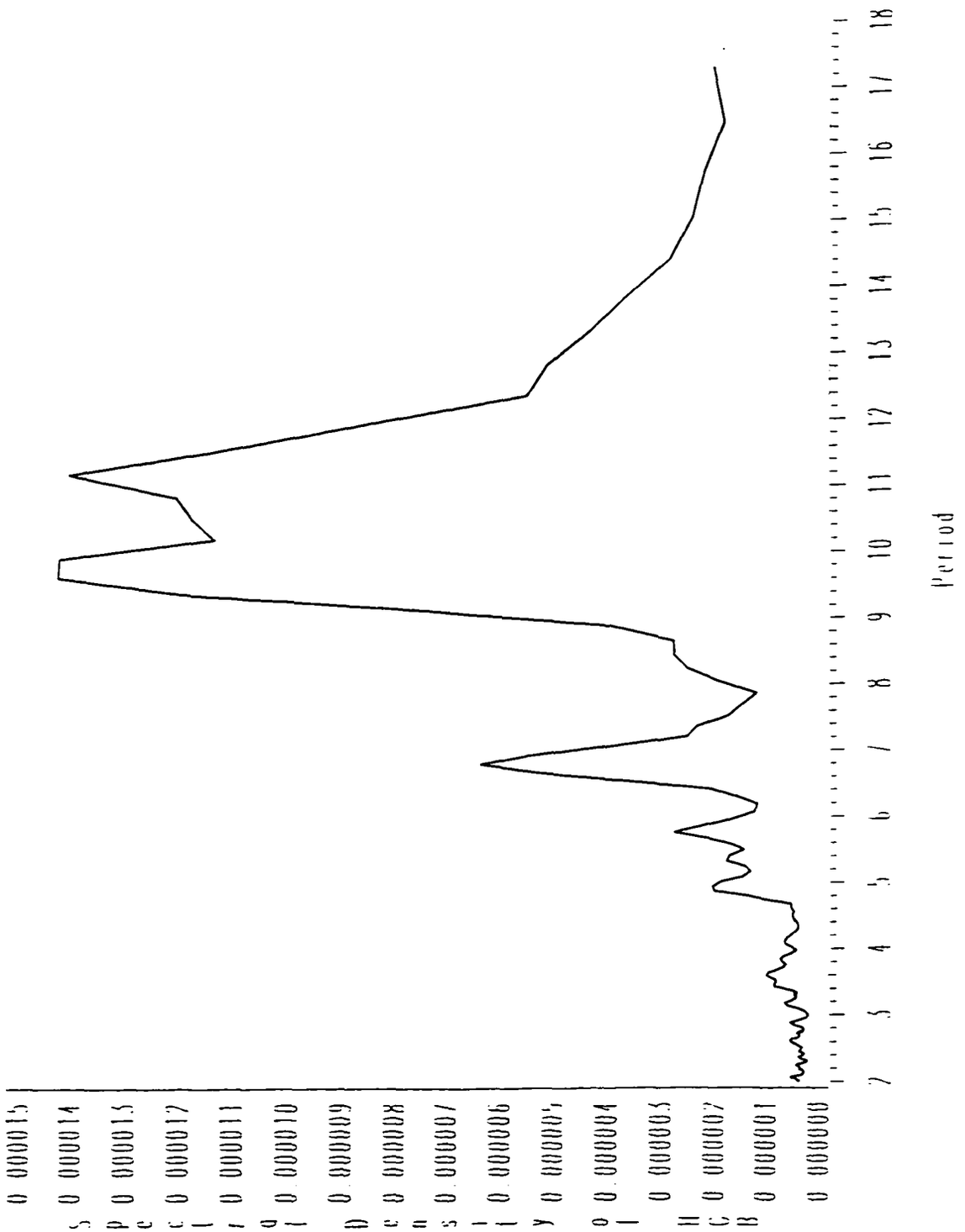

Figure 4. Representative Spectral Analysis Periodogram of Total Hemoglobin Data

Table 14. Wave-to-Wave Change in Wavelength (WWCW) Data[1]

Subject	Group	SIT WWCW	PSG WWCW
012	RLS	18.5	13.3
017	RLS	27.5	19.9
020	RLS	13.2	16.4
034	RLS	10.1	8.3
033	PLMS	27.0	11.9
026	RLS	18.6	18.4
030	RLS	12.2	14.3
052	PLMS	12.4	12.6
049	RLS	18.9	14.6
050	RLS	14.6	27.0
051	Control	18.1	18.7
054	Control	16.7	21.0
056	PLMS	24.8	17.4
057	RLS	18.3	18.9
055	Control	--	24.1
061	Control	23.3	19.4
060	PLMS	11.2	20.5
058	Control	9.2	11.6
059	Control	17.9	16.4
066	PLMS	27.8	27.9

(table cont'd)

Subject	Group	SIT WWCW	PSG WWCW
067	Control	17.6	17.4
068	Control	16.6	17.1
073	Control	19.8	21.7
070	Control	18.4	19.9
074	Control	21.4	19.9
069	PLMS	18.5	18.6

1) WWCW values are in seconds

Thus, in general, the "waves" in the rSO_2 data were not uniform and regular from wave to wave for most subjects.

Dual Recording Site Data

Three bald subjects were recruited into the study in an effort to find one or more bald subjects with PLMS. In all three subjects, two oximetry recording sites were used: one on the forehead, and one the vertex. The vertex site sensor was placed so that it would be as close as possible to the sensory/motor cortex for the legs. Although none of the three bald subjects had any significant sleep complaints, one of them was found to have PLMS (subject 069). There were technical problems with his forehead sensor just after the SIT, so the

polysomnogram was done with only the vertex recording site. This subject had a very stable vertex rSO_2 during both the SIT and PSG, and consequently, the majority of his PLMs (64%) occurred at stable rSO_2 points (see Tables 10 and 11 for this subjects' data on PLM occurrence in the rSO_2 and total hemoglobin wave cycles). For total hemoglobin, this subject had the majority of his PLMs at troughs (52.8%). Unfortunately, no other bald RLS or PLMS subjects could be recruited.

The use of two recording sites in these three subjects allowed for direct comparison of the data between the two recording sites. In order to determine if the rSO_2 and total hemoglobin readings were changing synchronously at the two sites, the number of peaks at each recording site were counted, and the number of "peak matches" was determined. These data are presented in Table 15. In general, the vertex sites had fewer peaks and were more stable than the forehead sites. In addition, there were relatively few peak matches, suggesting that in these three subjects, the rSO_2 and total hemoglobin at the two different sites were changing at least partly independently of each other. Correlations between the variables at the two different sites were also computed. These data are also presented in Table 15. One

Table 15. Dual Recording Site Data

Subj[1]	Test	Variable	Forehead Peaks	Vertex Peaks	No. of Matches	r
058	SIT	rSO_2	187	117	65	.34*
058	SIT	Hgb	202	197	29	.17*
058	PSG	rSO_2	158	110	5	-.01
058	PSG	Hgb	201	215	23	-.13*
070	SIT	rSO_2	99	35	17	.16*
070	SIT	Hgb	152	91	25	-.55*
070	PSG	rSO_2	87	29	21	.52*
070	PSG	Hgb	167	112	41	.39*
069	SIT	rSO_2	84	49	9	.82*
069	SIT	Hgb	135	123	36	.38*

1) Abbreviations are as follows: Subj = Subject, No. = Number, Hgb = Hemoglobin.
* $p < .0008$

subject (070) had two separate segments of PSG/sleep data; the correlations in Table 15 are for the first segment. The correlations for his second segment were -.16 for rSO_2, and -.61 for total hemoglobin. There were a total of 12 correlations performed on this data. This increased the number of statistical tests in the study to 65; thus, these correlations were not regarded as significant unless

they reached a p level of .0008 (which is .05 divided by 65). Ten of the twelve correlations reached this p level. This included nine of the ten correlations presented in Table 15, and the PSG-Hgb correlation from the second segment of sleep for subject 070. Although most of the correlations were highly significant, the majority of them accounted for only proportions of the variance. None-the-less, the presence of significant correlations between the two recording sites in rSO_2 and total hemoglobin indicated that these blood flow parameters were not completely independent of each other at the two recording sites.

Discussion

SIT and PSG Data

The first two hypotheses to be tested in the study concerned group differences on the SIT and PSG variables. Among the eleven SIT and PSG variables measured, the three that were most important were the SIT sensory and motor indices, and the PLM index. Differences on these variables were expected to occur because these variables were used (and are routinely used in clinical practice) to define the three groups. Of the nine possible pairwise comparisons among the three groups on these three variables, there were six directional predictions (see Table 2). Only three of these reached significance at the modified alpha level of 0.001, although the other three comparisons all reached p levels of 0.0037 or lower. The finding that one of these comparisons in particular, the RLS/PLMS comparison on the SIT sensory index, did not reach significance at the 0.001 level is surprising when the means of 50.3 (RLS) and 0 (PLMS) are considered. Although the low sample sizes of nine and six subjects were one obvious reason for the failure of these comparisons to reach significance at the specified p level, the low power that resulted from the selection of such a stringent initial alpha level of 0.001 was also to

blame. That decision could be criticized for lowering power to such an extent that it made the probability of making a Type II error unacceptably high. In addition, these comparisons were confirmatory of known phenomena (the nature of sleep in RLS and PLMS), not tests of novel hypotheses. That all were highly significant by typical standards, but not by the alpha correction based on experiment-wise error, indicates that the alpha correction procedure was excessively conservative and caused Type II error. This problem represents an example of the often discussed trade off between Type I and Type II error. Keppel (1991, p. 179) noted that "the concern for familywise error is usually expressed without regard for any increase in Type II error that may result". Keppel further suggested that if a researcher choose to limit the familywise (experiment-wise) Type I error rate by using an alpha correction procedure, then "I strongly urge your imaginative use of non-traditional values of FW to avoid losing substantial amounts of power" (Keppel, 1991, p. 180). He suggested cumulative Type I error rates of .10 and .25 as starting points for consideration. In the case of the three non-significant comparisons above, if a familywise error rate of .20 had been chosen (as per Keppel's recommendation), then the corrected alpha level

would have been .2 divided by 53 (or 0.0038) , and all three comparisons would have been regarded as significant. Therefore, those comparisons could be given more weight.

Of the eight remaining PSG variables, there were large differences in group means on two others: Sleep latency, and sleep efficiency (see Table 3). The group mean for the RLS group on sleep latency was strongly influenced by one subject who had a 6.5 hour sleep latency; however, because the Mann-Whitney test that was employed uses ranks, this outlier should not have unduly influenced the results. Again, the low sample sizes were most likely to blame. For sleep efficiency, the two comparisons involving the RLS group did achieve p levels lower than the traditional 0.05 level used for individual comparisons (.04 in the RLS/Control comparison, and .009 in RLS/PLMS comparison). In these two cases, it seems wise to follow another recommendation by Keppel (1991). In cases where the p level attained falls between the corrected alpha level chosen and the traditional 0.05 level, Keppel recommended that one should not make a formal decision regarding the null hypothesis (fail to reject H_o), but should instead decide to "suspend judgement". In this way, neither a Type I nor a Type II error is made.

In reviewing the group means for the other sleep variables, two other findings are noteworthy. First, the RLS group had a similar amount of slow wave sleep as the PLMS and control groups. This occurred despite the lower sleep efficiency in this group, and suggests that even though the total sleep time of RLS patients may be reduced because of their RLS symptoms, their PLMs during sleep (like those of the PLMS group) were not sufficiently disruptive to reduce slow wave sleep. There was also some evidence of a "first night effect" in the Control group, as evidenced by the high number of stage changes per hour of sleep (Anderson, 1998). The large number of sleep stage changes in the RLS and PLMS groups also illustrates the primary effect of PLMS, or perhaps a first night effect for all three groups.

Sensory and Motor Events in RLS Subjects

The next hypothesis concerned the temporal characteristics of the abnormal sensations of the RLS subjects during the SIT. It was predicted that the sensory events would be similar to PLMs in their temporal characteristics, and as such, would represent the waking analog of PLMs. The results did not confirm this hypothesis. Instead, the sensory events were found to be highly variable in their temporal characteristics among

different RLS subjects; only two of seven subjects had sensory events that met the scoring criteria used for PLMS.

The motor symptoms that were observed in the RLS subjects were also noteworthy. The observation that movements could become nearly continuous or be of very long duration when symptoms were severe is not consistent with the Periodic Cerebral Ischemia theory for at least two reasons. First, although RLS symptoms are precipitated by prolonged motor inactivity (during which B-wave activity should begin according to the PCI theory), the subsequent vigorous and long duration movements that occur when symptoms are severe should be sufficiently activating to both the cortex and brainstem that B-wave activity should be eliminated (i.e. the control of cerebral blood flow should revert to the waking mechanism of local flow-metabolism coupling). Second, if the motor symptoms in RLS are caused by cerebral ischemia, then that ischemia would have to be of relatively long duration to account for the observed motor symptoms, rather than periodic as suggested in the PCI theory. This would mean that some mechanism other than B-wave activity would have to be used to explain the observed motor symptoms in RLS. One possibility not previously discussed in this regard is

endothelin-induced vasospasm. The endothelins are peptides that are produced and released by endothelial cells; they are potent vasoconstrictors with a relatively long duration of action (see Cardell, Uddman, and Edvinsson, 1994, for a review). Endothelins are thought to play role in several cerebrovascular diseases, including migraine headaches and the vasospasm associated with subarachnoid hemorrhage. It has been shown that hemodynamic shear stress can stimulate the production of endothelin (Cardell et al., 1994). The turbulent blood flow that occurs near arterial bifurcations might be one source of such stress; thus, it is not unreasonable to suggest that vasospasm might be involved in RLS. This suggestion would represent a post hoc revision of the PCI theory.

The absence of PLMS in two of the RLS subjects, and the presence of only mild PLMS (PLMi = 15) in another subject who had severe waking symptoms, also deserves comment. Although this finding is consistent with previous work which has shown that only 80% of RLS subjects have PLMS when studied with a single night of polysomnography (Montplaisir et al., 1994), these previous studies have not specifically stated that PLMS could be absent when severe waking symptoms were present. Instead,

they seemed to imply that PLMS symptoms in patients with RLS could vary in severity (and even be absent) from night to night in much the same way that RLS symptoms vary from night to night. In the present study, two subjects who clearly had waking RLS symptoms did not have any PLMs while asleep. This finding is somewhat inconsistent with the PCI theory of RLS and PLMS because it is difficult to understand how the proposed B-wave induced periodic cerebral ischemia could present during wakefulness, then be absent as little as a few minutes later when the subject fell asleep. This finding (that PLMS can be absent even when severe RLS symptoms are present) brings into question the assumption that both RLS and PLMS are caused by the same pathogenic mechanism. This doubt is further strengthened by the lack of any clear periodicity in waking RLS sensory and motor symptoms noted in the present study. In addition, as pointed out in the introduction, the prevalence of PLMS has been found to be higher than normal in a fairly large number of medical conditions, including narcolepsy, uremia, organic impotence, and congestive heart failure to name a few. In one of these conditions in particular (congestive heart failure, CHF), a PLMS prevalence rate of 75% has been reported (Hanly and Zuberi-Khokhar, 1996). This is very

similar to the 80% value found in RLS subjects (Montplaisir et al., 1994). Thus, it is quite possible that RLS and PLMS may be caused by different pathologies, and that RLS is one of many conditions in which the pathology that causes PLMS is more common than normal. Future PLMS prevalence studies may help to clarify this issue.

Oximetry Data

There was essentially no support for the primary hypotheses of interest in the present study. The most important of these were the predictions that PLMs and SIT sensory and motor events would occur consistently at rSO_2 and total hemoglobin B-wave troughs. In fact, the opposite finding (i.e., that events tended to occur more frequently at peaks) occurred for all three event types (PLMs, SIT sensory events, and SIT motor events) for rSO_2, and for PLMs and SIT sensory events for total hemoglobin. For four event types (SIT Motor events in the rSO_2 cycle, and all three event types in the total hemoglobin cycle) a relatively large percentage of events also occurred at troughs. In order to further explore these results, and to determine if the percentages of events at the different wave limbs were significantly different from one another, a series of additional post hoc tests were performed (see

Appendix 4). Of the seventeen comparisons that were significant (out of a possible 48), twelve of them were comparisons in which percentages at peaks were higher than at other wave limbs, while five were comparisons in which percentages at troughs were higher than at other wave limbs. These tests also confirmed that the percentage of events at peaks was not significantly different from the percentage of events at troughs for five of the six comparisons (the peak/trough comparison was significant only for PLMs in the rSO_2 cycle). In addition, despite the fact the Chi Square tests were all highly significant, the failure of any event to occur at any one wave point (for either rSO_2 or total hemoglobin) more than 50 percent of the time casts additional doubt on whether or not the events were related in a causal way to cerebral oxyhemoglobin or total hemoglobin levels. One possible interpretation of this finding is that separate, but interconnected, brainstem centers may be responsible for generating RLS/PLMS symptoms and B-waves. If this were the case, then one center might be able to occasionally entrain the rhythm of the other center. This possibility has long been considered to be a potential mechanism by which Traube-Hering and Mayer waves might be generated (i.e. by influence from the respiratory centers on the

vasomotor center; see Koepchen, 1984, for a review). If this were the case, then the two phenomena of interest in the present study (PLMs and B-waves) would be expected to occur synchronously at some times, but not at others. The data obtained in this study are consistent with this idea. However, the idea of a brainstem center being directly responsible for the generation of PLMs is inconsistent with the idea that PLMs are spontaneous Babinski responses, because it has been shown that pyramidal tract damage is necessary and sufficient to elicit this reflex (van Gijn, 1978).

Another possibility that should be mentioned in regards to the wave cycle data concerns possible lags between arterial oxyhemoglobin levels and the variable actually measured by the NIRS equipment used in the present study. Because the NIRS instrument used in this study measures the hemoglobin oxygen saturation of all blood (including arterial and venous blood), and because about 70 percent of the cerebral blood is in the venous compartment, any lag between the arterial and venous compartments caused by circulation times could potentially influence the wave cycle data. Without simultaneous measurement of another cerebral blood flow parameter (such as blood flow velocity), it is impossible to know if the

waves measured by NIRS occur synchronously with waves measured by other techniques. Because the Somanetics instrument has only been F.D.A. approved in this country for just over two years, there are no studies directly investigating this issue; such a study would be very useful. The sampling rate of the Somanetics instrument (one sample per five seconds) was also problematical; this rate is inadequate for describing continuous brief phenomena such as B-wave peaks and troughs.

Another possibility in regards to the wave cycle data is that the critical physiologic parameter involved in the generation of PLMs and RLS symptoms might not be oxyhemoglobin saturation levels, but rather, CO_2 levels instead. CO_2 levels cannot be measured with NIRS, and may not correlate or vary synchronously with oxyhemoglobin levels.

It is worth emphasizing at this point that even if cerebral blood flow parameters are not related to PLMs and RLS symptoms, it might still be possible that a circulatory insufficiency occurring somewhere else within the nervous system (e.g. spinal cord, peripheral nerves) could be an underlying cause of either RLS symptoms, PLMS symptoms, or both. Adding substantial weight to this argument are the findings reviewed in the introduction

that are suggestive of a circulatory insufficiency (and resulting ischemia) as the cause of both disorders. These include the high prevalence of RLS and PLMS in anemia and conditions in which either anemia or circulatory problems are common, the transient nature of the symptoms (i.e. they are not continuously present throughout the day and RLS symptoms can be temporarily relieved by movement), and the improvement of RLS by treatment with drugs that either correct anemia or improve circulation (e.g. the dextran study by Parrow and Werner, 1966; and the sclerotherapy study in RLS patients with varicose veins by Kanter, 1995).

Despite the fact that PLMs and RLS sensory/motor events did not occur at any one point in the rSO_2 and total hemoglobin wave cycle with a high frequency (i.e. greater than 75% of the time), the finding that they tended to occur frequently at peaks is not only interesting, but is also at least partially consistent with the findings of several other recent studies. For example, Droste et al. (1996) used transcranial Doppler sonography to study B-wave activity in four PLMS patients. Although they did not assess where the PLMs occurred in the B-wave cycle, they did report that the blood flow velocity in the middle cerebral artery was significantly

higher in all four subjects when PLMs occurred (suggesting that they occurred at rSO_2 and total hemoglobin peaks) than at the midway points between PLMs. It would be very interesting to replicate their study, and conduct analyses similar to those used in the present study, assessing whether or not PLMs or RLS sensory/motor events occur consistently at any one point in the blood flow velocity B-wave cycle. In addition, both Montplaisir, Lapierre, and Lavigne (1994) and Parrino et al. (1996) have reported that PLMs occur in association with EEG arousal (as assessed by spectral analysis in the Montplaisir et al. study, and visual scoring of CAP cycles in the Parrino et al. study). It is likely that EEG arousal is associated with increased oxyhemoglobin levels (rSO_2 and total hemoglobin peaks), although the issue of whether or not the two variables are causally related remains unclear. Montplaisir et al. however, reported that waking RLS motor events were associated with EEG slowing (rather than arousal as was the case for PLMs). This EEG slowing during waking RLS movements is not consistent with the finding of increased higher oxyhemoglobin levels during these events that was found in the present study.

Given the failure to find a very consistent relationship between PLMs and RLS sensory/motor events and

the B-wave cycle in the present study, it is not surprising that the within subjects analyses comparing rSO_2 levels at event onset to non-event levels did not reach significance. The predictions for those comparisons were based on the prediction that the events would occur at very high rates at a single point in the B-wave cycle.

Wave Amplitudes, Wavelengths, and Spectral Analyses

As noted in the Results section, the B-wave amplitudes measured in the present study were much lower than expected. They were also much lower than the B-wave amplitudes found in transcranial Doppler sonography studies in normal subjects, which varied between 10 and 30 percent of the mean flow velocity in normal subjects (Diehl et al., 1991). One possible explanation for the low amplitudes observed in the present study again pertains to the predominately venous nature of the rSO_2 index measured by the Somanetics NIRS instrument. Because veins are not innervated nearly as much as arteries and arterioles, they have a much lower motility than do arteries and arterioles. Thus, the overall blood volume and oxygen saturations may change relatively little, while arterial blood volume and oxygen saturation change to a greater extent. The largest individual rSO_2 B-waves observed in any subject in the present study were about

ten percent of that subjects' mean rSO_2 level. This is one-third of the maximum amplitude of B-waves reported by Diehl et al. (1991). Thus, transcranial Doppler sonography may be a better tool than NIRS with which to measure B-wave activity.

The spectral analyses suggested that the waves observed in both the total hemoglobin and rSO_2 signals were characterized by a mixture of many different wavelengths. These included wavelengths in the traditional B-wave wavelength range of 50 to 70 seconds, and perhaps more importantly, a sizable number of wavelengths that were similar to the inter-movement-intervals typically associated with PLMS (i.e., 20 to 40 seconds). The large number of wavelengths detected by the spectral analyses in the present study is in partial contrast to the results of several other studies which have investigated the periodicity of B-waves. For example, in a transcranial Doppler sonography study Droste et al. (1993) found that six of ten normal subjects had a single B-wave wavelength (periodogram) peak in the 40 to 70 second range, while two subjects had two wavelength peaks in the 25 to 70 second range (one subject had peaks at 27 and 44 seconds, while the other had peaks at 29 and 67 seconds). In another transcranial Doppler study in

patients with normal pressure hydocephalus, Droste and Krauss (1993) showed a representative spectral analysis periodogram from one subject which had one large peak at about 50 seconds, and several smaller peaks in the 40 to 90 second range. In his study of B-waves in intracranial pressure tracings from neurological patients, Lundberg (1960) did not perform spectral analyses or other comprehensive quantitative analysis of B-wave wavelengths; however, he did report that the typical wavelength of B-waves was approximately one minute, and he also noted that waves with wavelengths in between those of the one-per-minute B-waves and the six-per-minute C waves did occasionally occur.

In the present study, waves in the 20 to 40 second wavelength range were generally more common than those in 40 to 70 second range. In addition, it was common for subjects to have four or more peaks in the entire 10 to 90 second range. These findings suggest that both (brainstem generated) B-waves and other waves reflective of regional cortical processes were present in the oximetry variables measured. Because NIRS measures oxygen saturation and blood flow in one small region of the brain, it can detect both processes. In addition, although cerebral vasomotor responsiveness to CO_2 is reduced during sleep, there is no

reason to believe that regional variations in cortical metabolic rate (and subsequent changes in regional cerebral blood flow and oxygenation) cease to occur during sleep. The relatively large number of different wavelengths observed in the present study is consistent with this dual-process explanation. Another possibility that could account for the large number of wavelengths observed is that B-wave wavelength may change during the course of the night (perhaps in relation to sleep stage). Thus, it is possible that a one hour segment of sleep may contain B-waves of several different predominant wavelengths, all of which would be detected by spectral analyses.

Still another possibility that might account for both the large number of wavelengths and the low wave amplitudes that were observed was suggested by the data on the wave-to-wave changes in wavelength. These data strongly suggested that the majority of subjects were not having (unambiguous) B-wave activity. The low amplitudes and variable wavelengths are exactly what would have been expected if no B-wave activity was present.

Dual Recording Site Data

The data from the three subjects whose oximetry variables were recorded from two sites was also not

consistent with the proposed PCI theory. In the one subject who had PLMs, these events did not tend occur at rSO_2 and/or total hemoglobin troughs. In fact, in this subject, the vertex rSO_2 and total hemoglobin were more stable than the forehead rSO_2 and total hemoglobin. In addition, the small percentage of peak matches between the two recording sites (and the relatively low correlations between them) indicated that B-wave activity was not present in these subjects. A high number of peak matches and high correlations would have been expected if B-waves were present.

Conclusions and Suggestions for Future Research

In summary, no support for the proposed Periodic Cerebral Ischemia theory was found in the present study. There were no group differences in B-wave amplitude, and perhaps more importantly, the RLS sensory/motor events and PLMs did not occur with a high frequency at the troughs in oxyhemoglobin wave cycle. Although these negative findings do not rule out the possibility of circulatory insufficiency as an underlying cause of RLS and PLMS, they do cast additional doubt on this general idea. Thus, it would be useful to replicate the previous studies that supported this hypothesis. These would include the treatment studies of Parrow and Werner (1966) and Kanter

(1995), in addition to prevalence studies in a fairly large number of patient groups (e.g. those with various kinds of circulatory problems). If treatment studies using blood thinners or vasodilators to treat RLS and PLMS cannot be justified (based on our current lack of knowledge concerning the pathogenesis of RLS and PLMS), then perhaps the prevalence of RLS and PLMS can be followed before and after treatment in patients who receive these drugs for other medical conditions. It would also be useful to extend the work of Droste et al. (1996) which found that B-waves in blood flow velocity were related to PLMs. The simultaneous use of transcranial Doppler sonography and cerebral oximetry in such a study would also be useful. The relationship of B-waves and PLMS could also be studied in neurological patients undergoing continuous monitoring of intracranial pressure as part of an evaluation of neurological disorders other than RLS or PLMS (e.g. head injury, hydrocephalus). If a relationship between cerebral blood flow oscillations and either RLS, PLMS, or both can be established, then treatment studies can be considered. Conversely, if such a relationship can be ruled out, then researchers can focus on other potential causes of, and treatments for, both of these disorders.

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Appendix 1 - Questionnaires Used in the Study

Restless Legs Questionnaire

Subject Number_____ Date_____

Date of Birth_____ Age_____ Sex_____

1) Please describe the problems you have with your legs.

2) Please describe the sensations in your legs in as much detail as you can.

3) At what times do you get the symptoms?

4) What do you do when you get the symptoms?

5) Which of the following activities are helpful in relieving your symptoms: (please check those that are helpful)

_____ Rubbing or massaging your legs
_____ Moving your legs while in bed
_____ Using a heating pad or taking a warm or hot bath
_____ Applying anything cold to the legs
_____ Stretching your legs
_____ Getting up and walking around
_____ Other (please describe below)

6) Which of the above activities are <u>most helpful</u> in relieving your symptoms?

7) How old were you when you first began to get the symptoms? _____

8) Have there been periods of time when the symptoms got better or worse or even went away completely? Please describe.

9) Are there any things which seem to make your symptoms better or worse? Please describe below:

10) Are your symptoms worse when you are under stress? (circle yes or no) YES NO

11) How often have you had the sensations in your legs over the past 6 months? Please check the most correct answer.

_____ One or two nights a week
_____ Three or four nights a week
_____ Five or six nights a week
_____ Every night of the week

12) Do you also get the sensations in your legs during the day? If yes, please note how many days a week you have had them over the last 6 months.

13) Please use the list below to indicate where the sensations occur. (Check all that apply)

_____ Feet
_____ Lower legs (between ankle and knees)
_____ Thighs
_____ Groin
_____ Trunk
_____ Shoulders or neck
_____ Upper arms
_____ Forearms
_____ Hands or fingers

14) Please use the list below to indicate what the sensations in your legs are most similar to. (Check all that apply)

_____ heat	_____ cramps or "Charlie horses"
_____ burning	_____ creeping or crawling
_____ cold	_____ pulling or stretching
_____ itching	_____ like your legs "falling asleep"
_____ aching	_____ painful
_____ numbness	_____ tingling

15) If the sensations are painful, please describe the pain below.

16) Do the sensations occur:
_____ on the surface of the skin
_____ just beneath the skin
_____ deep within the legs or muscles

17) Do you find that the sensations are difficult for you to describe? (circle yes or no) YES NO

18) Have you ever been told that your legs twitch, kick, or jump during the night? (circle yes or no) YES NO

19) Do you ever wake up and find that you have kicked the covers off the bed? (circle yes or no) YES NO

20) Do your legs or arms ever "jump" or "twitch" suddenly during the day? (circle yes or no). YES NO If yes, please describe.

21) Did your mother, father, or grandparents have restless legs or leg movements at night? Please circle the correct answer below, and indicate in the margin if they restless legs, leg movements, or both.

Mother.....	YES	NO	DON'T KNOW
Father.....	YES	NO	DON'T KNOW
Grandmother (mother's side).....	YES	NO	DON'T KNOW
Grandmother (father's side).....	YES	NO	DON'T KNOW
Grandfather (mother's side).....	YES	NO	DON'T KNOW
Grandfather (father's side).....	YES	NO	DON'T KNOW

22) Did any of your aunts or uncles have restless legs or leg movements at night? Please describe below.

23) Do any of your children or grandchildren have restless legs or leg movements at night? Please describe below, and be sure to indicate if your child or grandchild is a boy or girl. If you have no children or grandchildren please note that below.

24) Use the rating scale below to indicate how severe your restless legs symptoms usually are:

1 2 3 4 5 6 7

Mild Severe

25) Do you have difficulty falling asleep because of your symptoms? (circle yes or no) YES NO

26a) When you experience symptoms of restless legs, how long does it take you to fall asleep (on average)?_____minutes

26b) When you do not experience symptoms of restless leg, how long does it take you to fall asleep (on average)?_____

27) Do you wake up frequently during the night? (circle yes or no) YES NO

28a) When you experience symptoms of restless legs, how many hours do you sleep at night (on average)?_____hours

28b) How many hours do you sleep at night when you do not have symptoms of restless legs?_____hours.

29) Have you ever become depressed because of your restless legs? (circle yes or no) YES NO
If yes, have you been treated for your depression? YES NO

30) Have you ever sought treatment for your symptoms of restless legs (or leg movements at night)? (circle yes or no) YES NO

31) If yes, what treatment or medication did your doctor prescribe?

32) Was the treatment(s) effective?

33) Have you ever had a sleep study (polysomnogram) done? YES NO
If yes, what did your doctor tell you they had found?

34) Please list any other medications which you have taken in the past (even if they were not prescribed for you restless legs) which helped reduce your symptoms of restless legs:

35) Have you ever had moderately high or high fevers? YES NO
If yes, how did this affect your symptoms of restless legs?

36) Have you ever given blood? YES NO If yes, how did this affect your symptoms of restless legs?

37) How does excercise affect your symptoms of restless legs?

38) Do you get headaches? YES NO If YES, does anything in particular seem to cause you to have headaches?

39) If you are a woman, and have had children, how did your pregnancy affect your symptoms of restless legs?

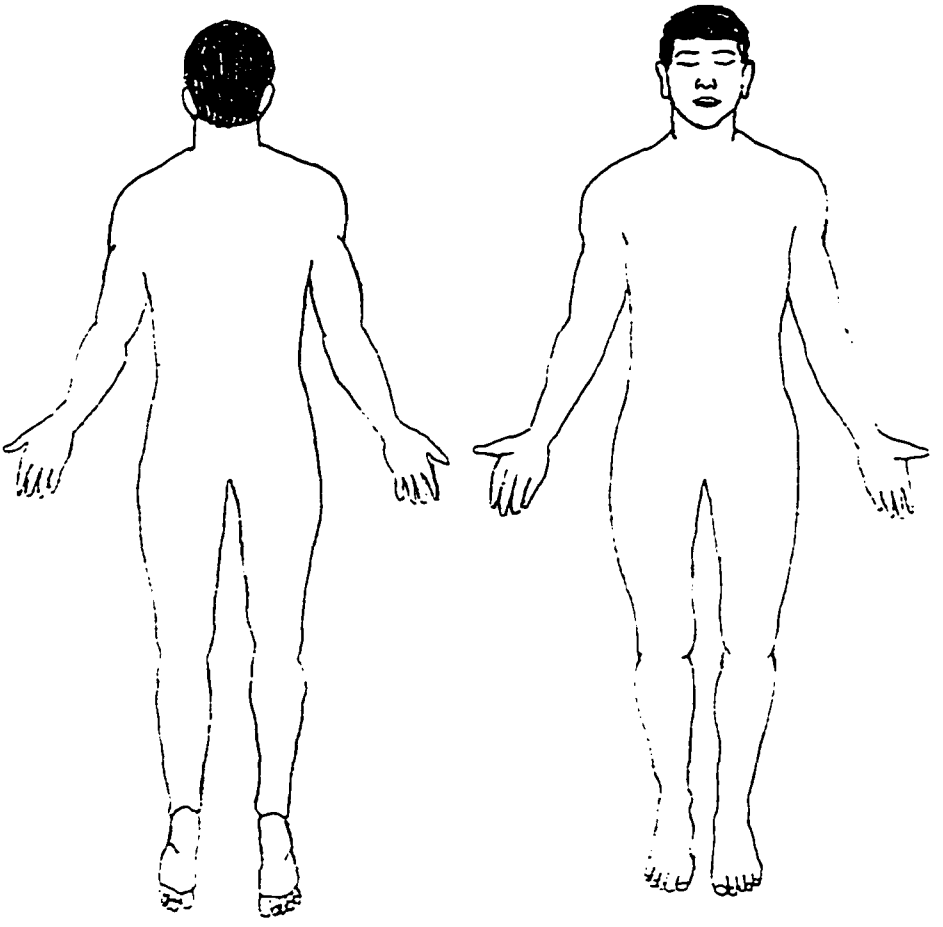
40) Please indicate if you have ever had any of the following diseases or conditions: (write in a "Y" for yes, or a "N" for no)

_____ anemia
_____ kidney disease/uremia
_____ iron deficiency
_____ chronic lung disease
_____ rheumatoid arthritis
_____ gastric (stomach) surgery
_____ circulatory problems
_____ heart disease
_____ leukemia
_____ spinal cord\back injury
_____ any other serious illness (list below)

_____ stroke or head injury
_____ high blood pressure
_____ low blood pressure
_____ leg cramps
_____ fibromyitis/fibrositis
_____ diabetes
_____ neurological disease
_____ cold hands, legs, feet
_____ weakness in legs\arms
_____ headaches

41) Would you be willing to participate in any future research projects that we conduct (circle yes or no) YES NO

42) On the figures below please fill in the areas where your restless legs sensations occur.



Thank you for completing this questionnaire

SLEEP DISORDERS INVENTORY

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INSTRUCTIONS

*** The Sleep Disorders Inventory is a questionnaire that is designed to obtain information that will assist in the description and diagnosis of a patient's sleep disorder. It also provides information that is helpful in determining the causes and the correct treatment of a patient's sleep disorder.

*** Please answer these questions to the best of your ability. It is understood that some of your answers will be approximations, not exact. Such estimates are acceptable. Also, a few of the questions may require information from a person who has observed your sleep. If you have access to such information, feel free to use it.

*** If you are asked to give a YES__NO answer, and you are not certain of your response, give the answer that is closest to the truth as best you can determine. If you are asked to give a numerical answer, such as the number of minutes it takes you to fall asleep, and you are not certain, give an approximate answer that is closest to the truth as best you can determine.

*** Please answer ALL of the questions. If a YES__NO item does not apply to you, answer NO. If you encounter an item that calls for a numerical response and it does not apply to you, or you cannot give an estimate, the number 0 will indicate that it does not apply or that you cannot estimate.

*** Before beginning the Sleep Disorders Inventory, please provide the following information:

NAME: _____ DATE: _____

SOCIAL SECURITY NUMBER: _____ CLINIC NUMBER: _____

AGE: _____ WEIGHT: _____ HEIGHT: _____

THE SLEEP DISORDERS INVENTORY BEGINS ON THE NEXT PAGE.

SLEEP DISORDERS INVENTORY

* Please CIRCLE the appropriate response for each of the YES or NO questions. Please FILL IN THE BLANK with the correct number for each question that is followed by a blank.

1. Do you have difficulty falling asleep at night ?..... YES NO
   If NO, go to # 2
   (a) About how many nights does this happen each week ?.....
   (b) On nights when you have this problem, how many minutes does it take you to fall asleep ?.....
   (c) On nights when you have this problem, how many hours do you sleep ?.....

2. Do you wake up during the night and have difficulty falling back to sleep ?..... YES NO
   If NO, go to # 3
   (a) About how many nights does this happen each week ?.....
   (b) On the average, how many times do you wake up each night ?.....
   (c) How many minutes does it take you to fall asleep after awakening ?.....
   (d) On nights when you have this problem, how many hours do you sleep ?.....

3. Do you wake up in the morning before your scheduled wake time, and cannot return to sleep ?..... YES NO
   If NO, go to # 4
   (a) How many nights per week do you have this problem ?.....
   (b) On nights when you have this problem, how many hours do you sleep ?.....

4. Do you wake up during the night frequently, but fall asleep soon afterwards ?... YES NO
   If NO, go to # 5
   (a) How many times a night do you wake up ?.....
   (b) How many nights each week do you have this problem ?.....

5. On nights when you do not have any problem falling asleep or regaining sleep, how many minutes does it usually take you to fall asleep ?.....

6. How many nights each week do you have sleep loss of any kind ?.....

7. How many hours do you sleep on your best nights ?.....

8. On nights when you do not have any problem falling asleep or regaining sleep, how many hours do you usually sleep ?.....

9. Does lack of sleep often cause you to fall asleep at inappropriate times or in the wrong place during the day ?..... YES NO

10. Does lack of sleep often cause you to have trouble functioning during the day ?. YES NO

11. Does your bed partner disturb your sleep at night ?..... YES NO
    If NO, go to # 12
    (a) Does this cause you sleep loss some of the time ?..... YES NO
    (b) Is this why you lose sleep most of the time ?..... YES NO

12. Is your sleep disturbed by environmental factors such as traffic, neighbors or family members ?..... YES NO
    If NO, go to # 13
    (a) Does this cause you sleep loss some of the time ?..... YES NO
    (b) Is this why you lose sleep most of the time ?..... YES NO

13. Is your bedroom dark enough for sleep at night ?..... YES NO
    If YES, go to # 14
    (a) Does this cause you sleep loss some of the time ?..... YES NO
    (b) Is this why you lose sleep most of the time ?..... YES NO

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14. Is your bedroom temperature comfortable enough for sleep at night ?.....YES NO
If YES, go to # 15
(a) Does this cause you sleep loss some of the time ?.....YES NO
(b) Is this why you lose sleep most of the time ?.....YES NO

15. Do you sleep enough hours but have trouble waking up, feeling unrefreshed ?.....YES NO

16. Do you sleep enough hours but fall asleep involuntarily during the day, but only when relatively unstimulated (like watching tv) ?.....YES NO

17. Do you sleep enough hours but fall asleep involuntarily during the day, even when doing something very important (like driving) ?.....YES NO

18. Do you sleep enough hours but still have trouble functioning during the day ?...YES NO

19. How many nights per month do you:
_____ Snore loudly and persistently
_____ Thrash about while asleep (but are not dreaming)
_____ Gasp or snort while asleep
_____ Stop breathing while asleep
_____ Wake up in the night and feel unable to breathe

20. How many mornings a month do you awaken with a headache ?.....

21. Do you wake up from a sound sleep repeatedly because your legs jerk ?.....YES NO
If YES: Are your leg movements frequent, vigorous and regular ?.....YES NO
If YES: How many nights per month does this occur ?.....

22. Is your sleep ever delayed because your legs feel restless or odd in bed ?.....YES NO
If NO, go to # 23
(a) Do you need to move your legs in bed, or get up and move to fall asleep ?...YES NO
(b) How many nights per month do you legs feel this way ?.....

23. Do you have sudden and compelling attacks of sleepiness, so bad you must stop what you are doing and sleep ?.....YES NO
If NO, go to # 24
(a) How many minutes do you sleep (nap) when you have such an attack ?.....
(b) Do you awaken from you nap feeling refreshed ?.....YES NO
(c) How many times each month does this occur ?.....

24. When you are startled, emotional, excited, or happy do you often experience extreme weakness (for example, in your legs) or drop things ?.....YES NO

25. When you are startled, emotional, excited, or happy do you collapse (fall) ?....YES NO
If YES: Are you still aware of your surroundings ?.....YES NO

26. As you fall asleep or wake up, do you often see things that are not there ?.....YES NO
If YES: Is what you see very clear and realistic ?.....YES NO
How many nights each month ?.....

27. As you fall asleep or wake up, do you often feel unable to move (paralyzed) ?...YES NO
If YES: How many nights each month ?.....

28. On how many nights have nightmares awakened you in the last month ?.....
If ANY: How intense are they: 1=Mild, 2=Frightening, 3=Terrifying ?.....

29. Do you often move violently during your sleep while dreaming, and sometimes even hurt yourself or your partner by accident, or fall out of bed ?.....YES NO
If YES: How many times in the last month has this happened ?.....

SLEEP DISORDERS INVENTORY

30. Do you awaken from a deep sleep sweating, your heart beating fast or pounding, with a feeling of fear but with no memory of a dream ?.....YES NO
If NO, go to # 31
(a) How many times in the last month has this happened ?.....
(b) How intense is this experience: 1=Mild, 2=Frightening, 3=Terrifying ?.....
(c) Do you have similar experiences during the day as well ?.....YES NO

31. Do you walk in your sleep ?.....YES NO
If NO, go to # 32
(a) How many times a month does this happen ?.....
(b) About how many minutes pass by while you are sleepwalking ?.....

32. Do you often talk in your sleep ?.....YES NO

33. Do you often grind your teeth in your sleep ?.....YES NO

34. How many times per night do you wake up specifically to use the bathroom ?.....

35. How many nights per week do you wake up with indigestion or heartburn ?.....

36. Do you often eat your last meal or a large snack within 2 hours of bedtime ?....YES NO

37. Do you often do vigorous exercise within an hour of bedtime ?.....YES NO

38. How many glasses (bottles/cans) of alcoholic drink do you have each day ?.....

39. How many nights each month do you use alcohol to aid sleep ?.....

40. How many cups or glasses of caffeinated beverages do you drink in a day ?.....

41. How many days a week do you drink caffeinated beverages after 7 p.m. ?.....

42. How many cigarettes a day do you smoke ?.....

43. Do you take any medications that contain caffeine or stimulants, such as allergy medications, nasal decongestants, or pain killers ?.....YES NO
If YES: How many minutes before trying to sleep do you take them ?.....

44. Is your sleep problem caused or made worse by physical discomfort or pain:
____ Never; ____ Rarely; ____ Sometimes; ____ Often; ____ Most or All of the Time.

45. Do you ever work night shifts (Any 8-12 hour shift starting 6 pm to 12 am) ?....YES NO
If YES: How many nights per month ?.....
How many times a month do your work hours change ?.....

46. Do you work at home after 8:00 p.m. ?.....YES NO
If YES: How many nights per week ?.....

47. Do you sacrifice sleep time in order to get in more work or family time ? ..YES NO
If YES: How many hours per night ?.....
How many nights per week ?.....

48. On weekends or your days off, do you often sleep more than an hour later than your usual wake up time ?.....YES NO

50. When you have sleep problems, do you:
(a) Often go to bed earlier to make up for lost or unrefreshing sleep ?.....YES NO
(b) Often wake up later to make up for lost or unrefreshing sleep ?.....YES NO
(c) Get up out of bed and: ___watch TV; ___read; ___eat; ___work CHECK ALL THAT APPLY
(d) Take naps during normal waking hours ?.....YES NO

If NO naps, go to # 51
(1) How many times per week do you take naps ?.....
(2) How many minutes are your naps, on average ?.....
(3) Do you awaken from your naps refreshed ?.....YES NO

51. Is your sleep problem worse when you are under stress ?.....YES NO
Do you sleep better when you sleep away from home ?.....YES NO

52. Have you been under noteworthy stress recently ?.....YES NO

53. When you try to sleep, does worrying or problem solving often keep you awake ?..YES NO
Do you often worry about getting enough sleep to function the next day ?.....YES NO
Do you often get frustrated and angry about not getting to sleep ?.....YES NO

54. Do you worry too much in general ?.....YES NO

55. Does your sleep problem affect your mood during the day ?.....YES NO

56. Are you currently diagnosed as having a mood disorder (depression) ?..... YES NO

57. Are you currently diagnosed as having an anxiety disorder ?.....YES NO

58. Have you ever been treated for mental/emotional/drug/alcohol problems ?.....YES NO
If YES: Have you ever been hospitalized for such problems ?.....YES NO

59. How long have you had your sleep problem ? ____No. Years _____No. Months _____No. Weeks

60. Have you previously received non-drug treatment for sleep problems ?.....YES NO

61. Have you recently taken any prescription or over-the-counter medication for sleep problems ?.....YES NO
If NO, go to # 62
(a) How many nights a week do you usually take this medication ?.....
(b) How many months have you been taking sleep medication ?.....

62. Please list which medications you are now taking and the condition for which each is being taken. Include prescription and over-the-counter medications.

	MEDICATION	CONDITION		MEDICATION	CONDITION
1			4		
2			5		
3			6		

63. Please list any medications you have recently stopped taking and the condition for which each was being taken. Include prescription and over-the-counter medications.

	MEDICATION	CONDITION		MEDICATION	CONDITION
1			3		
2			4		

64. Is there anything you would like to clarify or add, that might be helpful ? You may write your comments below and on the reverse side of this page:

*** THANK YOU FOR COMPLETING THIS INVENTORY ***

DAILY SLEEP DIARY

Subject Number_____ Date_____

PLEASE RESPOND TO THESE QUESIONS SOON AFTER YOU WAKE UP FOR THE DAY.

1. About what time did you first try to fall asleep last night?_____

2. Approximately how many minutes did it take you to fall asleep?_____

3. If you awoke from sleep last night, please indicate about how long it took you to get back to sleep.

_____min _____min _____min _____min _____min

_____min _____min _____min _____min _____min

4. About what time did you awaken for the day this morning?_____

5. About how many hours did you sleep altogether last night?_____

6. How difficult was it for you to fall asleep last night?

1 2 3 4 5

Not very difficult — Extremely difficult

7. How rested do you feel this morning?

1 2 3 4 5

Very Rested — Poorly Rested

8. Rate the quality of last night's sleep.

1 2 3 4 5

Excellent — Very Poor

9. What was your level of physical tension when you went to bed last night?

1 2 3 4 5

Extremely Relaxed — Extremely Tense

10. Rate your level of mental activity when you went to bed last night.

1 2 3 4 5

Very Quiet — Very Active

Daily Sleepiness Scale

Form D

Name_____ Date_____

Instructions: Please answer questions 1 - 14 before you go to bed tonight. Before answering these questions, think about how sleepy you felt today. Then, read each question carefully, and circle the letter or number of the one answer that best applies to you. Please answer question 15 when you wake up in the morning.

1) About how many hours did you sleep last night?

(a) 5 hours or less
(b) 5 ½ hours
(c) 6 hours
(d) 6 ½ hours
(e) 7 hours
(f) 7 ½ hours
(g) 8 hours
(h) 8 ½ hours
(i) 9 hours
(j) 9 ½ hours or more

2) What was the overall quality of your sleep last night?

1 2 3 4 5

Very Poor Excellent

3) How difficult was it for you to awaken this morning?

1 2 3 4 5

Not at all difficult Very difficult

4) How often did you experience a strong desire to lay down and sleep today?

1 2 3 4 5

Almost never Very Often

5) How many times did you "nod off" (or fall asleep for just a few seconds) today while you were engaged in unimportant activities (for example, while watching TV or reading)?

(a) None
(b) Once
(c) Twice
(d) Three times
(e) Four or more times

6) How many times did you "nod off" (or fall asleep for just a few seconds) today while you were engaged in important activities (for example, while driving or having a conversation)?

(a) None
(b) Once
(c) Twice
(d) Three times
(e) Four or more times

7) About how many minutes did you nap today?

(a) none
(b) 1 to 20 minutes
(c) 21 to 40 minutes
(d) 41 to 60 minutes
(e) 61 minutes or more

8) How often did you do things to help yourself stay awake today? For example: move around or exercise,... wash your face or take a shower,... drink coffee or other caffeinated beverage, etc..

1 2 3 4 5

Almost never Very Often

9) How much did sleepiness negatively affect your job performance or normal activities today?

1 2 3 4 5

Not at All Very Much

10) How often did you have trouble concentrating or paying attention today?

1 2 3 4 5

Almost never Very Often

11) How much did you yawn today?

1 2 3 4 5

Almost never Very Often

12) How often did your eyes feel tired, heavy, or droopy today?

1 2 3 4 5

Almost never Very Often

13) How often did you feel physically tired or fatigued (but not necessarily sleepy) today?

1 2 3 4 5

Almost never Very Often

14) Overall, how sleepy were you today?

1 2 3 4 5

Not at all sleepy Very sleepy

Please answer this last question when you wake up in the morning.

15) About how long did it take you to fall asleep last night?

(a) 0 to 5 minutes
(b) 6 to 15 minutes
(c) 16 to 30 minutes
(d) 31 to 60 minutes
(e) 61 or more minutes

Thank you for completing this questionnaire!

Appendix 2 - Study Consent Form

LOUISIANA STATE UNIVERSITY-BATON ROUGE CAMPUS
Consent Form

1. Study Title: Cerebral Hemoglobin Oxygen Saturation in Patients with Restless Legs Syndrome and Periodic Limb Movements in Sleep.

2. Performance Sites: Louisiana State University

3. Investigators: The following investigators are available for questions at the phone numbers listed below.

Name:	William Waters, Ph.D.
Department:	Psychology
Telephone Number:	388-4115
Name:	Mark Hurry, M.A.
Department:	Psychology
Telephone Number:	766-6399

4. Purpose of Study: To determine if symptoms of Restless Legs Syndrome and Periodic Limb Movement Disorder are associated with abnormalities in blood flow and oxygen transport to the brain.

5. Patient Inclusion: The study includes three groups of subjects aged 18 to 80 years old: patients with Restless Legs Syndrome, patients with Periodic Limb Movements in Sleep, and healthy control subjects. Each group will consist of 12 to 15 subjects.

6. Patient Exclusion: Persons younger than 18 or older than 80 years old, persons with any sleep disorder other than Restless Legs Syndrome or Periodic Limb Movements in Sleep, persons with any neurological disorder, life-threatening medical condition, or mentally disabling medical disorder.

7. Description of the Study: This study consists of two parts. Part One is a screening process that begins with a phone interview lasting about ten minutes. The purpose of the phone interview is to make an initial decision about whether or not you meet the inclusion criteria for the study. If you do, you will be sent a consent form and packet of questionnaires to complete. After you have received the packet, you will again be contacted by phone so that the study and consent form can be explained to you. This should take about ten or fifteen minutes. The questionnaires include the Sleep Disorders Inventory, which should take about 20 minutes to complete. Participants with Restless

Legs Syndrome will also fill out a questionnaire called the Restless Legs Questionnaire; this should take about 20 minutes to complete. In addition, each subject will be required to complete two short questionnaires, the Daily Sleep Diary and the Daily Sleepiness Scale, each day for a period of two weeks. Each of these questionnaires takes about five minutes to complete each day. After you have returned the questionnaires, they will be reviewed, and, according to the results, you may or may not qualify for Part Two of the study.

Part Two of the study will require you to undergo a one hour test during which you will try not to move your legs (Suggested Immobilization Test), and then undergo an overnight sleep study on the same night. Both tests will be conducted in the L.S.U. Department of Psychology's sleep laboratory in Audubon Hall, which is located on L.S.U.'s Baton Rouge campus. For some subjects the Suggested Immobilization Test will consist of 30 minutes of attempting to remain still, followed by 15 minutes of walking in place, and then an additional 30 minutes of attempting to remain still. During the Suggested Immobilization Test and the overnight sleep study, blood flow to the brain will be measured by a small sensor placed on the forehead. Brain activity, eye movements, muscle tone, heart rate, breathing, and leg movements will also be measured during these tests using sensors attached to the surface of the skin. It will take about one hour and fifteen minutes to attach the recording sensors, so subjects will be required to arrive at the sleep laboratory two and half hours prior to their normal bedtime, or at about 8:00 p.m.. Subjects will be awakened at 6:00 a.m. in the morning, and should be ready to leave about 30 minutes later.

8. Benefits: The study will not benefit all subjects directly, though some subjects may choose to have their results sent to their physician. The study will benefit subjects by helping physicians understand the causes of Restless Legs Syndrome and Periodic Limb Movement Disorder, and by enabling researchers to target more specific and effective treatments for their disorders.

9. Risks: The risks are very small, and include a small possibility of developing mild skin rashes where recording devices are attached to the skin. Patients with Restless Legs Syndrome and Periodic Limb Movement Disorder who withdraw from medications being used to treat their disorder may experience increased difficulty in falling asleep, a decrease in the quality of their sleep, and an increase in daytime sleepiness. Patients with Restless Legs Syndrome and Periodic Limb Movement Disorder who withdraw from

medical treatment will be required to do this under the supervision of their physician.

10. Alternatives: This study does not evaluate any treatment for Restless Legs Syndrome or Periodic Limb Movement Disorder. Alternative methods for measuring blood flow to the brain include transcranial Doppler sonography, which is technically difficult, and various types of "brain scans", which are both costly and invasive.

11. Removal: Subjects who agree to participate will fulfill all of the study requirements when the overnight sleep study is completed, or when they return the questionnaires to us if they do not qualify for Part Two of the study.

12. Right to Refuse: Subjects may choose NOT to participate or withdraw from the study at any time with no penalty.

13. Privacy: The results of the study may be published as group data in which no subjects' results are presented individually. The privacy of participating subjects will be protected and the identity of participants will not be revealed. The data collected will not be used for any purpose not approved by the participants and the L.S.U. Institutional Review Board.

14. Release of Information: The questionnaires and recordings for participants in this study will be reviewed by the investigators, but the identity of the participants will not be revealed. If any participant wishes to have results from their overnight sleep study (or any other results from the study) sent to their physician, they may do so by filling out a written request for information form at their physician's office, or by sending a written request to:

William Waters, Ph.D.
Department of Psychology
236 Audubon Hall
Louisiana State University
Baton Rouge, LA 70803

15. Financial Information: There are no costs to participants in the study other than any travel costs that might be incurred in coming to LSU for the overnight sleep study.

16. Signatures:

The study has been discussed with me and my questions have been answered. I understand that additional questions regarding the study should be directed to investigators listed above. I understand that if I have questions about subject rights, or other concerns, I can contact Charles E. Graham, Chairman, Institutional Review Board (504-388-1492). I agree with the terms above and acknowledge I have been given a copy of the consent form.

Signature of Study Participant_____ Date_____

Witness_____ Date_____

Investigator_____ Date_____

The study subject has indicated to me that she or he is unable to read. I certify that I have read this consent form to the subject an explained that by completing the signature line above the subject has agreed to participate.

Signature of Reader_____ Date_____

Appendix 3 - Scoring Rules for B-Wave Cycle Data

1) The waves in the rSO_2 and total hemoglobin data should be thought of as consisting of three equal parts: troughs, ascending/descending limbs, and peaks. If the trough to peak (ascending part of wave) and peak to trough (descending part of wave) are not equal in height, divide each segment into equal thirds as described above.

2) To determine wave limb in the rSO_2 waves, use the following guidelines:

a) If the wave height is 1 rSO_2 point, there are only peaks & troughs.

b) If the wave height is 2 rSO_2 points, the bottom points are troughs, the middle ones are either ascending or descending, and the top points are peaks.

c) If the wave height is 3 rSO_2 points, the bottom points are troughs, the two middle ones on each limb are either ascending or descending, and the top points are peaks.

d) If the wave height is 4 rSO_2 points, the two bottom points are troughs, the one middle point is either ascending or descending, and the two top points are peaks.

e) If the wave height is 5 rSO_2 points, the two bottom points are troughs, the two middle points are either ascending or descending, and the two top points are peaks.

f) If the wave height is 6 rSO_2 points, the two bottom points are troughs, the three middle points are either ascending or descending, and the two top points are peaks.

3) Stable points can occur whenever the rSO_2 value does not change for 5 or more data points. Whenever there are five or more data points at the same rSO_2 level, the first two points after the increase or decrease are scored as either peaks or troughs (peaks if the previous point was lower, and troughs if the previous point was higher). Similarly, the last two points before the next increase or decrease are scored as either peaks or troughs (peaks if the next point is lower, and troughs if the next point is higher). All points in the middle are scored as stable (this can be as few as one data point).

Appendix 4 - Additional Statistical Tests on B-Wave Cycle and Periodogram Peak Data

This appendix contains a number of additional statistical tests on the event occurrence in the B-wave cycle and spectral analysis periodogram peak data. These tests were done on a post hoc basis to help clarify the results. There were a total of 68 of these tests (48 pairwise comparisons on the wave cycle data, 14 Chi Square tests on the periodogram peak data, and six ANOVAs on the mean number of periodogram peaks among the groups). An initial alpha level of .004 was used to assess the significance of these tests. This reflects the number of tests (68) divided into an overall alpha level of .25). The .25 overall alpha level was used as per the recommendations of Keppel (1991). In addition, the multistage Bonferroni correction procedure of Larzelere and Mulaik (1977) was used. There were 16 tests that reached significance in the first step of this multi-stage procedure, and one test that reached significance (at the .005 p level) in the second step of this procedure.

The data presented in Tables 6 through 11 in the Results section are summarized in Table A4-1, which lists the group means for the percentages of events (SIT sensory, SIT motor, and PLMs) occurring at each point in

Table A4-1. Summary of B-Wave Cycle Data (Percent of Events Occurring at each Point in the Cycle)

Event	Trough	Ascend	Peak	Descend	Stable
			rSO_2 Data		
Sensory	19.4	7.0	48.6	11.4	13.6
Motor	30.4	7.7	38.9	12.8	10.2
PLMs	18.9	8.8	48.3	10.1	14.0
			Total Hemoglobin Data		
Sensory	35.9	7.6	42.0	14.4	--
Motor	40.6	11.2	35.1	13.2	--
PLMs	33.9	12.8	40.3	12.9	--

the rSO_2 and total hemoglobin B-wave cycles. The SIT sensory and motor event means are for RLS subjects only, while the PLMS means are for the thirteen subjects who had PLMs (seven RLS and six PLMS subjects). These data were assessed for normality with Shapiro-Wilk tests, and for homogeneity of variance (within each row in Table A4-1) with Levene tests for homogeneity of variance. The Shapiro-Wilk tests were significant, indicating non-normal distributions, for three means: the ascending limb for SIT sensory events in the rSO_2 cycle, and the descending

and stable limbs for PLMs in the rSO_2 cycle. The Levene tests for homogeneity of variance were significant for SIT motor events in the total hemoglobin cycle and PLMs in the total hemoglobin cycle. Differences among the means (within each row) in Table A4-1 were assessed with paired-sample t-tests whenever both means were normally distributed and had homogeneity of variance, and Wilcoxin tests whenever the comparison involved any non-normally distributed mean or pair of means with unequal variances. The t values and Wilcoxin z values, and their associated p values, for these pairwise comparisons are listed in Table A4-2 (for rSO_2 data) and Table A4-3 (for total hemoglobin data). For SIT sensory events in the rSO_2 B-wave cycle, the percentage of events occurring at peaks was significantly higher than the percentage of events occurring at descending or stable limbs. For SIT motor events in the rSO_2 B-wave cycle, the percentages of events occurring at peaks was significantly higher than the percentages occurring at ascending, descending, and stable limbs. The same pattern was seen for the percentage of events occurring at the troughs, while the peak/trough comparison was not significant. For PLMs in the rSO_2 B-wave cycle, the percentage of PLMs occurring at the peaks was significantly higher than the percentages of PLMs

Table A4-2. Summary of Pairwise Comparisons on rSO_2 B-Wave Data

	Comparison[1]									
Event[2]	P/T	P/A	P/D	P/S	T/A	T/D	T/S	A/D	A/S	D/S
Sens	-3.04	-2.37	4.83	4.40	-2.37	1.86	0.82	-1.35	-1.01	-0.32
	(n.s.)	(n.s.)	(.003)	(.005)	(n.s.)	(n.s.)	(n.s.)	(n.s.)	(n.s.)	(n.s.)
Mot	-1.24	-5.25	7.47	4.68	9.43	4.04	4.75	-1.68	-0.62	0.50
	(n.s.)	(.001)	(.001)	(.002)	(.001)	(.004)	(.001)	(n.s.)	(n.s.)	(n.s.)
PLMs	-5.01	-11.37	-3.18	-2.62	2.67	-2.13	-1.88	-0.53	-0.47	-0.24
	(.001)	(.001)	(.002)	(n.s.)	(n.s.)	(n.s.)	(n.s.)	(n.s.)	(n.s.)	(n.s.)

1) Abbreviations are as follows: T = Trough, A = Ascending, P = Peak, D = Descending, S = Stable

2) Abbreviations are as follows: Sens = Sensory, Mot = Motor

Table A4-3. Summary of Pairwise Comparisons on Total Hemoglobin B-wave Data

	Comparison[1]					
Event	P/T	P/A	P/D	T/A	T/D	A/D
Sensory	-0.79	-6.42	4.61	4.22	2.90	-2.86
	(n.s.)	(.001)	(.004)	(n.s.)	(n.s.)	(n.s.)
Motor	-0.53	-2.67	-2.67	-2.67	-2.67	-0.71
	(n.s.)	(n.s.)	(n.s.)	(n.s.)	(n.s.)	(n.s.)
PLMs	-0.66	-3.18	-3.18	-2.90	-3.18	-0.20
	(n.s.)	(.002)	(.002)	(.004)	(.002)	(n.s.)

1) Abbreviations are as follows: T = Trough, A = Ascending, P = Peak, D = Descending

occurring at troughs, ascending limbs, and descending limbs.

For SIT sensory events in the total hemoglobin B-wave cycle, the percentage of events occurring at the peaks was significantly greater than the percentages of events occurring at the ascending or descending limbs. There were no significant pairwise comparisons for the SIT motor event occurrence in the B-wave cycle. For the PLM occurrence in the total hemoglobin B-wave cycle, the

percentages of events occurring at both peaks and troughs was significantly greater than the percentages of events occurring at the ascending and descending limbs.

In summary, of the seventeen comparisons above that were significant, twelve were comparisons in which the percentage of events occurring at the peak was greater than the percentages occurring at other wave limbs, while five were comparisons in which the percentage of events occurring at the troughs was greater than the percentages occurring at the other wave limbs. Only one of the peak/trough comparisons was significant (for PLMs in the rSO_2 B-wave cycle).

In Table 12 (see the Results section), the number of periodogram peaks in the different wavelength ranges for all three groups during the SIT were presented. A total of six Chi-Square tests were done on these data to determine if the observed frequencies were significantly different from equal frequencies in all ranges. None of these tests reached significance at the .004 p level.

In Table 13 (see Results section), the number of periodogram peaks in the control subjects and in all subjects with PLMs during sleep were presented. A total of four Chi Square tests were run on these data to determine if the observed frequencies were significantly

different from equal frequencies in each range. None of these four tests reached significance at the .004 p level.

In addition, four Chi-Square tests of homogeneity were run to determine if the groups differed significantly in their frequencies in the different ranges (one test each for rSO_2 and total hemoglobin data during both the SIT and PSG). None of these tests reached significance at the .004 p level.

Four ANOVAs were run on the group means for the number of periodogram peaks per subject (one each for rSO_2 and total hemoglobin during both the SIT and PSG) to determine if there were any group differences in the number of periodogram peaks. None of these four ANOVAs reached significance at the .004 p level.

Finally, two ANOVAs were run on the group means for the wave-to-wave change in wavelength data (see Table 14) to determine if the groups differed on this variable. Neither of these two ANOVAs reached significance at the .004 p level.

Vita

The author, Mark Hurry, was born in Baton Rouge, Louisiana, on September 18, 1965. He resided in Baton Rouge until 1973, when his family moved to LaPlace, Louisiana. He attended grade school at St. Joan of Arc Catholic School in LaPlace, and high school at St. Charles Catholic High School in LaPlace. After completing high school in 1983, he enrolled at Louisiana State University in the fall of 1983. He was awarded the Bachelor of Science degree in Psychology in May of 1988. Following graduation he worked for two years as a research associate for Gareth Parry, M.D., in the Department of Neurology at Louisiana State University Medical School in New Orleans, Louisiana. He began graduate school in the Clinical Psychology program at Louisiana State University in the fall of 1990, and was awarded the Master of Arts degree in Psychology in December, 1994.

DOCTORAL EXAMINATION AND DISSERTATION REPORT

Candidate: Mark J. Hurry

Major Field: Psychology

Title of Dissertation: Cerebral Hemoglobin Oxygen Saturation in Patients with Restless Legs Syndrome and Periodic Limb Movements in Sleep

Approved:

Major Professor and Chairman

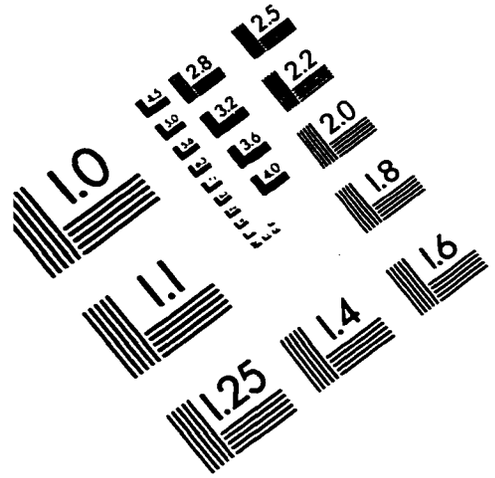
Dean of the Graduate School

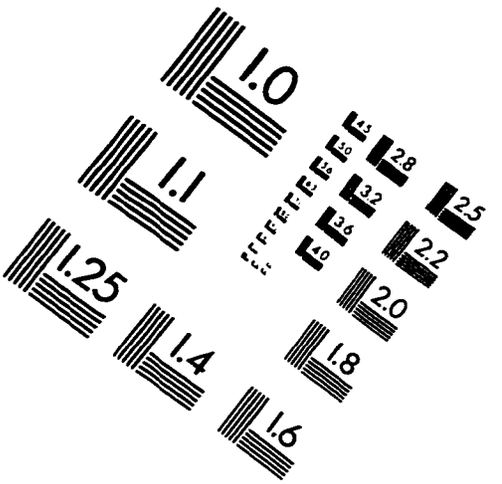
EXAMINING COMMITTEE:

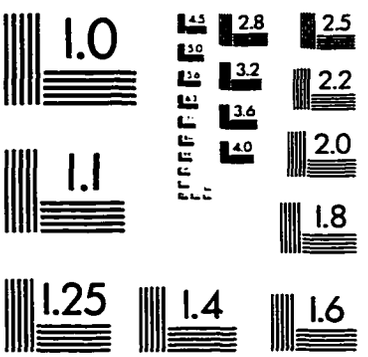
Date of Examination:

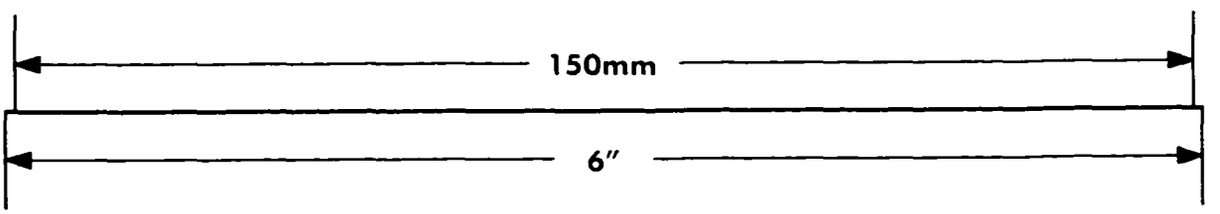
July, 28, 1998

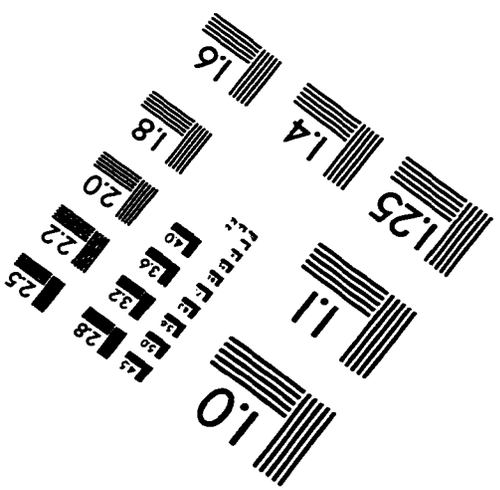
IMAGE EVALUATION TEST TARGET (QA-3)

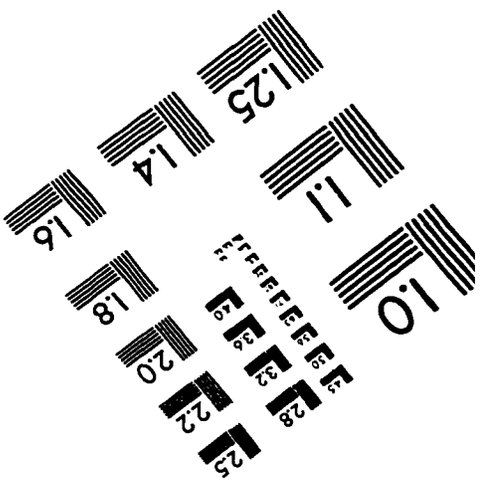












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